

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

|   |   |                                |
|---|---|--------------------------------|
| In re Application of: <b>Robert Patrick Hof</b> | ) | Confirmation No. <b>7528</b>   |
|   | ) |                                |
| Application No. <b>10/501,250</b>               | ) | Group Art Unit: <b>1625</b>    |
|   | ) |                                |
| Filing Date: <b>December 6, 2004</b>            | ) | Examiner: <b>Taofiq Solola</b> |
|   | ) |                                |
| For: <b>Process for the Preparation of</b>      | ) |                                |
| <b>2-(6-Substituted-1,3-Dioxane-4-yl)</b>       | ) |                                |
| <b>Acetic Acid Derivatives</b>                  | ) | <u>Date: November 2, 2009</u>  |

**APPELLANTS' BRIEF UNDER 37 C.F.R. § 41.37**

This brief is being filed in the above-identified patent application in furtherance of a Notice of Appeal filed on September 1, 2009. A fee of \$540.00 as required under 37 C.F.R. §41.20(b)(2) is being filed concurrently herewith. Because the period for filing the appeal brief extends through November 1, 2009, no extensions of time are believed to be necessary. In view of November 1 falling on a Sunday, this brief is being timely filed on Monday, November 2 under the next business day rule.

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**2.     The Real Party in Interest**

The real party in interest in this appeal is AstraZeneca UK Limited of London, England.

**3. Related Appeals and Interferences**

Appellants are not aware of any other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

**4. Status of Claims**

The status of the claims is as follows upon filing of this Appeal Brief:

Claims pending: 1 to 8

Claims objected to: None

Claims allowed: None

Claims rejected: 1 to 8

The claims on appeal are 1 to 8.

**5.     Status of Amendments**

Appellants filed an Amendment and Response under 37 C.F.R. 1.312 on January 4, 2007 in which originally filed claims 1, 3, 7 and 8 were amended. The U.S. Patent Office subsequently withdrew the application from issue and sent a non-final Office Action dated April 18, 2007 in which the amendments were entered but the rejection of all claims (1 to 8) was asserted. No subsequent amendments to the claims have been made. As such, Appellants submit that claims 1 to 8 as listed herein in the claims appendix are the currently pending claims of record.

**6. Summary of Claimed Subject Matter**

An aspect of Appellants' present invention relates generally to a process for the preparation of a 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivative according to formula 1. In accordance with an exemplary embodiment of the invention as recited in independent claim 1, the process comprises the preparation of a 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivative according to formula 1 from its corresponding 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivative according to formula 2 in the presence of a phase transfer catalyst according to formula 3 and an ion according to formula 4 containing an oxyllating agent. This aspect of Appellants' invention is described in the specification at, *inter alia*, paragraphs [0005], [0006], [0007] and [0008] of the published U.S. application.

7. **Grounds of Rejection to be Reviewed on Appeal**

Whether claims 1 to 8 are unpatentable under 35 U.S.C. § 103(a) as obvious over EP 1024139 to Kizaki *et al.* (“Kizaki”) in view of Am. Inst. Chem. Eng. J. (1998) 44(3): 612-646 to Naik *et al.* (“Naik”).

The Examiner notes that Appellants claim a process that employs a phosphonium phase transfer catalyst. According to the Examiner, Kizaki teaches a similar process that uses an ammonium phase transfer catalyst and Naik teaches that ammonium phase transfer catalysts and phosphonium phase transfer catalysts are well known and commonly used. Based on these characterizations of Kizaki and Naik, the Examiner asserts that one of ordinary skill in the art would have known to substitute the ammonium phase transfer catalyst used in the Kizaki process with a phosphonium phase transfer catalyst to arrive at Appellants’ claimed invention. In addressing Appellants’ submission in a response filed on August 20, 2007 that Naik fails to teach that ammonium and phosphonium catalysts may be used interchangeably, the Examiner, in the Final Office Action dated September 19, 2007, cited KSR Int’l Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007) (“KSR”) as effectively dispensing with this argument,

...because their recognition as phase transfer catalysts creates an obvious to try situation, and applicant’s invention confirms that they are in fact interchangeable. (page 3 of Final Office Action)

The Examiner also cited MPEP 2144.06 in asserting that

...the issue is not whether two equivalents are recognized as interchangeable, if equivalency is recognized in the prior art, it is obvious to substitute one for the other. The recognition of the catalysts as equivalents by Naik *et al.*, creates an obvious to try situation for applicant. (page 3 of Final Office Action)

The aforementioned grounds for rejection were maintained in the most recent Final Office Action dated June 1, 2009.

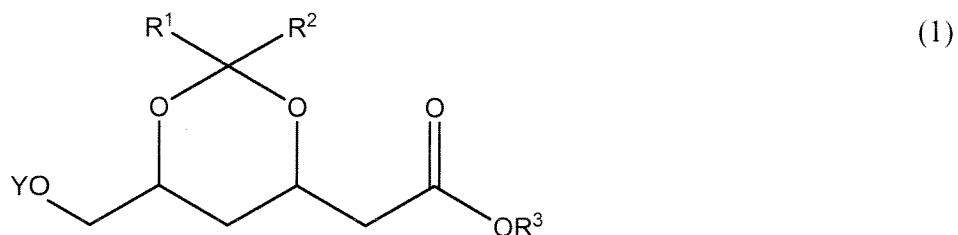


**8. Argument**

Appellants respectfully submit that the rejection of claims 1 to 8 under 35 U.S.C. § 103(a) is improper and should be reversed.

**A. Independent Claim 1**

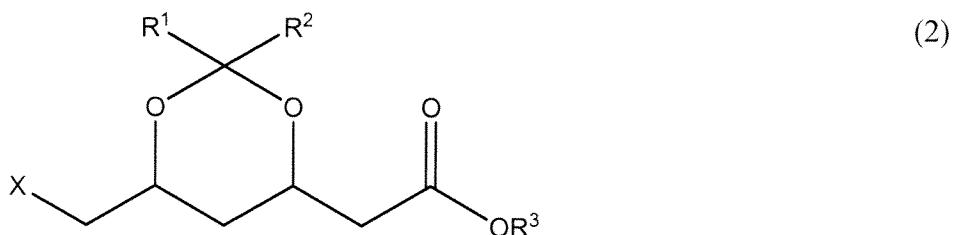
With respect to independent claim 1, Appellants respectfully submit that the applied references do not teach or suggest a process for the preparation of a 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivative according to formula 1,



wherein

**R<sup>1</sup>**, **R<sup>2</sup>** and **R<sup>3</sup>** are each independently a C1-4 alkyl group or wherein **R<sup>1</sup>** and **R<sup>2</sup>** together with the C-atom to which they are bound form a 5- or 6-membered cycloalkyl and **Y** stands for **R<sup>A</sup>**-CO- or for **R<sup>B</sup>**-SO<sub>2</sub>- where **R<sup>A</sup>**, **R<sup>B</sup>** are chosen from the group of alkyl or aryl with 1-12 C-atoms,

from its corresponding 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivative according to formula 2,



wherein

**R<sup>1</sup>**, **R<sup>2</sup>** and **R<sup>3</sup>** are as defined above and

X stands for a halogen,

in the presence of a phase transfer catalyst and an oxyating agent, characterized in that a quaternary phosphonium ion according to formula 3,



wherein

$\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$  each independently stand for an alkyl, cycloalkyl, aralkyl or aryl with 1 to 12 C-atoms,

is used as a phase transfer catalyst and an ion according to formula 4,



wherein Y is as defined above, is used as an oxyating agent.

#### Rejection of Claim 1 under 35 U.S.C. 103(a) over Kizaki in view of Naik

The Examiner's rejection appears to be based on a presumption of equivalence between the ammonium and phosphonium catalysts that is supposedly taught by Naik and an interpretation of KSR that Appellants submit is unduly narrow and does not accurately reflect the totality of the Court's ruling. Appellants refer to the following passage from KSR upon which the Examiner appears to rely for support of his "obvious to try" rejection:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of

innovation but of ordinary skill and common sense. (KSR at 1732)

Appellants submit that, as discussed below, (1) Naik does not teach that ammonium phase transfer catalysts and phosphonium phase transfer catalysts are equivalent and (2) the “obvious to try” test as defined in KSR has not been satisfied by the facts of the subject application.

(1) Naik does not teach that ammonium phase transfer catalysts and phosphonium phase transfer catalysts are equivalent

Naik is directed to a review of phase transfer catalysts and methods of modeling phase transfer catalyst reactions. Several classes of catalysts are listed, including ammonium phase transfer catalysts and phosphonium phase transfer catalysts. However, while Naik describes these catalysts as finding application in a range of industrial procedures, Naik does not teach or suggest that they may be used interchangeably in any specific process. On the contrary, Naik emphasizes the differences between ammonium phase transfer catalysts and phosphonium phase transfer catalysts, including differences in their relative stabilities and activities, as represented in Table 1 of Naik at page 615, reproduced below for convenience:

Table 1. Commonly Used PT Catalysts

| Catalyst          | Cost                         | Stability and Activity  | Use and Recovery of Catalyst  |
|-------------------|------------------------------|---|---|
| Ammonium salts    | Cheap                        | Moderately stable under basic conditions and up to 100°C. Decomposition by Hofmann elimination under basic conditions. Moderately active. | Widely used. Recovery is relatively difficult.  |
| Phosphonium salts | Costlier than ammonium salts | More stable thermally than ammonium salts, although less stable under basic conditions.   | Widely used. Recovery is relatively difficult.  |
| Crown ethers      | Expensive                    | Stable and highly active catalysts under basic conditions and at higher temperatures up to even 150-200°C.                                | Often used. Recovery is difficult and poses environmental issues due to their toxicity.                   |
| Cryptands         | Expensive                    | Stable and highly reactive, except in the presence of strong acids.   | Used sometimes despite high costs and toxicity, due to higher reactivity.                                 |
| PEG               | Very cheap                   | More stable than quaternary ammonium salts, but lower activity.   | Often used. Can be used when larger quantities of catalyst cause no problems. Relatively easy to recover. |

As shown in Table 1 above, Naik teaches that phosphonium phase transfer catalysts are less stable under basic reaction conditions than ammonium phase transfer catalysts, but are otherwise more stable thermally than ammonium phase transfer catalysts.

Naik makes it clear that the selection of a phase transfer catalyst for a particular objective is typically decided by using an empirical approach in which catalysts are screened to determine their suitability for that particular objective. Appellants point to the section on page 615 of Naik entitled "Choice of PT catalyst" and the sentence bridging columns 1 and 2 on page 615, which states that

[a]lthough no definite guidelines can be given to select the best catalyst for a given reaction system, analysis based on some of these factors [stability under reaction conditions, ease of preparation or availability of catalyst, ease of separation or recovery, activity and toxicity] can provide a suitable methodology to screen different PT catalysts for a given system.

This teaching of an experimental approach to choosing a phase transfer (“PT”) catalyst with the proper characteristics is reinforced by the statement made in Naik that “the exact choice of catalyst depends on the system under consideration” (top of column 1 on page 616 of Naik) and by the suggested screening procedure involving catalysts under consideration. Accordingly, a person of ordinary skill in the art would not have an expectation of success from a reading of Naik to simply substitute an ammonium phase transfer catalyst with a phosphonium phase transfer catalyst in a given reaction.

The Examiner asserts that the issue is not whether the ammonium catalysts and phosphonium catalysts are interchangeable, but whether it would be obvious to substitute one for the other. Appellants disagree and submit that a demonstrated lack of interchangeability between two classes of phase transfer catalysts would directly influence whether a person of ordinary skill in the art would consider it obvious to substitute a phase transfer catalyst from one class with a phase transfer catalyst from another class. As detailed above, Naik teaches that there are physicochemical differences between ammonium phase transfer catalysts and phosphonium phase transfer catalysts. Appellants submit that this teaching would prevent a person of ordinary skill in the art from considering ammonium phase transfer catalysts and phosphonium phase transfer catalysts to be interchangeable in a particular chemical reaction or class of reactions. Accordingly, Appellants submit that it would not be obvious to substitute the ammonium phase transfer catalyst described in the Kizaki process with a phosphonium phase transfer catalyst as described in Naik.

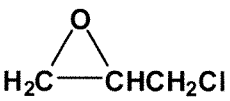
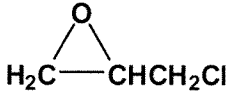
(2) The “obvious to try” test as defined in KSR has not been satisfied in the subject application

*A. Lack of identified, predictable solutions*

The Supreme Court's indication that obviousness exists where the solutions are predictable and where a person of ordinary skill would have good reason to pursue the known options has not been satisfied in the subject application. As discussed in section (1) above, simple substitution of an ammonium phase transfer catalyst with a phosphonium phase transfer catalyst in a particular chemical reaction or class of reactions would not lead to a predictable result and as such, a person of ordinary skill in the art would not have good reason to make this change without further evidence of potential success.

Appellants refer to their previously submitted reference by Starks (*i.e.*, Phase Transfer Catalysis, Principles and Techniques by C.M. Starks; Academic Press (1978)) ("Starks") (attached as Exhibit A), in which all successful reactions involving carboxylate ion displacement were carried out in the presence of ammonium phase transfer catalysts. On the few occasions where phosphonium phase transfer catalysts were used, no ester product was found to be present, as shown in Table 21 at pages 142-146 of Starks. The portions of Table 21 that relate to phosphonium salts are reproduced below for convenience.

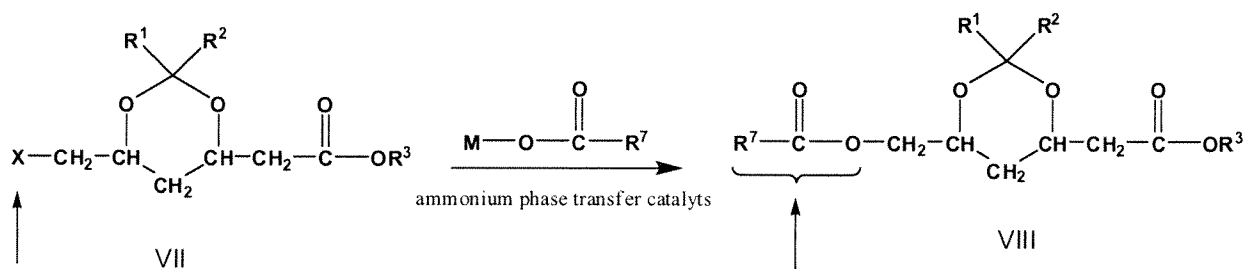
Table 21 (selected entries of Phase Transfer Catalyzed Ester Syntheses)

| <u>Acid</u>  | <u>RX</u>   | <u>Catalyst</u>                         | <u>Product<br/>(Yield, %)</u> |
|--|---|---|-------------------------------|
| $\text{CH}_2=\text{CHCO}_2\text{H}$                    |  | Quaternary phosphonium salts            | Ester (-)                     |
| $\text{CH}_2=\text{C}(\text{CH}_3)\text{CO}_2\text{H}$ |  | $(\text{CH}_3)_4\text{N}^+ \text{Cl}^-$ | Ester (91.3)                  |
|  |   | Phosphonium salts                       | Ester (-)                     |

As can be seen from the table entries above, the reaction of chloromethyl-containing substrates with carboxylic acids in the presence of phosphonium phase transfer catalysts did not result in the production of any measurable ester product. In contrast,

in a direct comparison of an ammonium phase transfer catalyst with a phosphonium phase transfer catalyst, the reaction that employed the ammonium catalyst resulted in a 91.3% yield of desired ester product, while the reaction that employed the phosphonium catalyst did not provide any measurable amount of ester product. Thus, Starks actually teaches away from the substitution of ammonium phase transfer catalysts with phosphonium phase transfer catalysts in reactions that are similar to those recited in Appellants' claim 1. Because the teaching from Starks appears in a textbook rather than in a periodical, Appellants submit that it could be argued that this teaching more closely represents the common general knowledge of a person of ordinary skill in this art.

Further, in U.S. Patent No. 5,594,153 (a copy of which was also previously submitted for the Examiner's review) ("the '153 patent") (attached as Exhibit B), the reaction of step (d), as depicted below (and as described at column 6, lines 1-12 of the '153 patent), can be viewed as similar to the process claimed by Appellants in the subject application. For this procedure, ammonium phase transfer catalysts are the catalysts of choice (see, *e.g.*, the '153 patent at column 6, lines 21 to 31; column 13, lines 56-60; column 15, line 16; column 16, line 62; and column 20, line 46).



There is absolutely no teaching or suggestion that the reaction of step (d) should be conducted in the presence of phosphonium phase transfer catalysts.

The previously submitted Halpern review article (Phase Transfer Catalysis Communications (1997) 3:1, 1-12) ("Halpern") (attached as Exhibit C) also supports the choice of ammonium phase transfer catalysts for esterification reactions, which is the type of reaction recited in Appellants' claim 1. Halpern describes ammonium phase

transfer catalysts with different ligands (see, *e.g.*, the definitions of TBAB, Aliquat 336<sup>®</sup> and TEBAc provided on page 1), but there is no teaching or suggestion of any catalyst other than an ammonium-containing catalyst for use in an esterification reaction.

The results provided in Halpern clearly illustrate how simply varying the nature of a ligand on a catalyst can have a dramatic effect on the result achieved. The effects resulting from a more fundamental change in the catalyst – namely, changing the core nitrogen atom with a phosphorus atom – would be expected to have an even more dramatic effect, and so a person of ordinary skill in the art would not be, as a matter of procedure, likely to pursue this option in the absence of persuasive data of comparable achieved results. Thus, Halpern can be viewed as teaching away from the casual substitution of ammonium catalysts with phosphonium catalysts.

If a sampling of other art in this technical area is viewed, it becomes apparent that, in relation to the reaction systems that are the focus of the subject application, ammonium phase transfer catalysts are the catalysts of choice. Bram *et al.* in Tetrahedron Letters (1982) 23, 5407-5408 and in Israel Journal of Chemistry (1985) 26, 291-298 (copies of which were previously submitted for the Examiner's consideration) (attached as Exhibits D and E, respectively), describe the catalysis of alkylation reactions generally, and in all cases, the catalysts used are ammonium-containing catalysts.

As an aside, Appellants note that a phosphonium salt is listed in Table 10 on page 296 of the Israel Journal of Chemistry article for a completely different class of reaction (*i.e.*, a dehydrohalogenation of a simple haloalkane) than the one recited in Appellants' claim 1. It is worth pointing out, however, that the results obtained for this reaction differ significantly depending whether a phosphonium salt is used (high reaction temperature required with only moderate yield – entry 1) or an ammonium salt is used (low reaction temperature with high yields – entries 9 and 11-13).

Kizaki teaches the use of an ammonium phase transfer catalyst because it clearly directs a person of ordinary skill in the art toward the use of tetra n-butylammonium halides as a phase transfer catalyst for esterification reactions (see,



*e.g.*, Examples 7 and 8 of Kizaki). Appellants submit that a person of ordinary skill in the art reading Kizaki would presume that the selection of an ammonium phase transfer catalyst was the culmination of screening and/or optimization procedures and therefore would not have been motivated by a reasonable expectation of success to replace the ammonium phase transfer catalyst with a completely different class of catalyst (such as phosphonium phase transfer catalysts) for which there is no prior art teaching of equivalence, as alleged by the Examiner. Appellants submit that the Examiner is engaging in prohibited hindsight analysis in asserting, against the teaching of Naik, Kizaki and the general state of the art at the time of the filing of Appellants' application (as represented by the attached exhibits), that a person of ordinary skill in the art would substitute the relatively cheap and effective ammonium phase transfer catalyst of Kizaki with a costlier phosphonium phase transfer catalyst for which there is no reasonable expectation of success for accomplishing the same objective.

*B. No design need or market pressure to solve a problem*

According to KSR, the circumstances under which an "obvious to try" situation arises requires "a design need or market pressure to solve a problem...." That situation does not exist in the subject application. Kizaki provides no suggestion that are any problems associated with the use of ammonium phase transfer catalysts in the described processes that would provoke a search for alternative catalysts. In fact, to the contrary, Kizaki proclaims that the inventors' discovery of "the use of a less expensive quaternary ammonium salt in a smaller amount" constitutes a "novel reaction technology" (page 16, paragraph [0078]). Therefore, Appellants submit that a person of ordinary skill would not be motivated to rely on Naik, which, as discussed above, describes the differences in outcome that can exist between phosphonium phase transfer catalysts and ammonium phase transfer catalysts as well as the fact that phosphonium phase transfer catalysts are more expensive than ammonium phase transfer catalysts (see *e.g.*, Table 1 of Naik), in replacing the less expensive ammonium phase transfer catalyst of Kizaki with a costlier phosphonium phase transfer catalyst.

Kizaki reports a yield of 81% of desired product using 1.0 equivalents (based on the chloromethyl-containing starting material) of an ammonium phase transfer catalyst. This yield drops to 70% when only 0.5 equivalents of the ammonium phase transfer catalyst is used (see Examples 7 and 8, respectively, at page 21, line 45 to page 22, line 19 of Kizaki). In contrast to these results, Appellants discovered that in using the phosphonium catalysts recited in Appellants' claim 1, good yields were achievable using a substantially lower amount of catalyst. For example, use of only 0.1 equivalents (based on the chloromethyl-containing starting material) of a phosphonium phase transfer catalyst provided a yield of desired product of 77.2% (see Example 3 at paragraph [0028] of Appellants' published application). Thus, in a comparison of an example described by Kizaki with an example from Appellants' specification, Appellants were able to achieve a higher yield of desired product (77% vs. 70%) using only 20% as much catalyst as taught by Kizaki.

At least in view of the above discussion, Appellants submit that a person of ordinary skill in the art would not consider replacing the ammonium phase transfer catalyst of Kizaki with a phosphonium phase transfer catalyst as suggested by the Examiner. Accordingly, Appellants believe that the claims of the subject application should be acknowledged as nonobvious over the combination of Kizaki and Naik.

#### B. Dependent Claims 2 to 8

Appellants respectfully assert that dependent claims 2 to 8 are individually allowable at least because of their respective dependencies from independent claim 1 and for the reasons set forth above. Thus, the rejection of dependent claims 2 to 8 is improper and should be reversed.

Kizaki and Naik, either alone or in combination, do not teach or suggest claim 2, which depends from claim 1 and further limits the process to wherein  $R^A$  and  $R^B$  are chosen from the group of  $C_1$ - $C_4$  alkyl or aryl with 6-10 C-atoms.

Kizaki and Naik, either alone or in combination, do not teach or suggest claim 3, which depends from claim 1 and further limits the process to a quaternary phosphonium salt according to formula 3a as the phase transfer catalyst, wherein

$R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are as defined in claim 1, A stands for a halogen, and an acid salt according to formula 4a is used as the oxyating agent, wherein Y is as defined in claim 1 and M stands for alkali metal or an alkaline metal.

Kizaki and Naik, either alone or in combination, do not teach or suggest claim 4, which depends directly from claim 3 and indirectly from claim 1, and further limits the process in that the quaternary phosphonium salt according to formula 3a is used in a molar equivalent amount of 0.05 to 0.7 relative to the amount of compound according to formula 2.

Kizaki and Naik, either alone or in combination, do not teach or suggest claim 5, which depends directly from claim 4 and indirectly from claim 1, and further limits the process in that the quaternary phosphonium salt according to formula 3a is used in a molar equivalent amount of 0.1 to 0.5 relative to the amount of compound according to formula 2.

Kizaki and Naik, either alone or in combination, do not teach or suggest claim 6, which depends from any one of claims 1-5 and further limits the process in that the process is carried out at a temperature between 100 and 160° C.

Kizaki and Naik, either alone or in combination, do not teach or suggest claim 7, which depends from any one of claims 1-5 and further limits the process in that the process is carried out at a temperature between 110 and 150° C.

Kizaki and Naik, either alone or in combination, do not teach or suggest claim 8, which depends from any one of claims 1-5 and further limits the process in that the compound according to formula 1 is tert-butyl 2-[(4R,6S)-2,2 dimethyl-6-[(methyl-carbonyloxy)methyl]-1,3-dioxan-4-yl] acetate and in that the compound according to formula 2 is tert-butyl 2-[(4R,6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate.

In view of the foregoing, Appellants respectfully request the reversal of the Examiner's rejections and the allowance of the pending claims. If there are any other fees due in connection with the filing of this Appellants' Brief, please charge the fees to our Deposit Account No. 50-0310.


If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account No. 50-0310.

Respectfully submitted,

**MORGAN LEWIS & BOCKIUS LLP**

Dated: **November 2, 2009**

By:

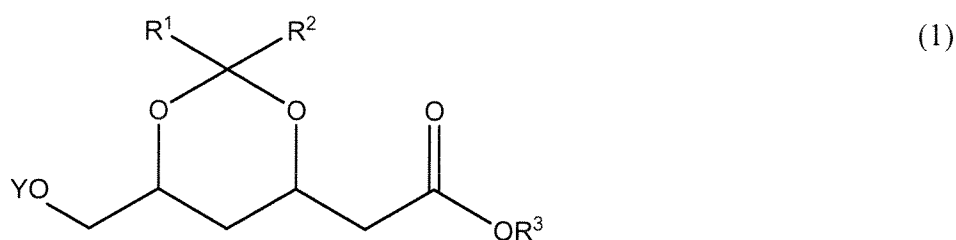
  
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## 9. Claims Appendix

Subsequent to entry of the Amendment and Response under 37 C.F.R. § 1.312 as filed on January 4, 2007, the claims read as follows:

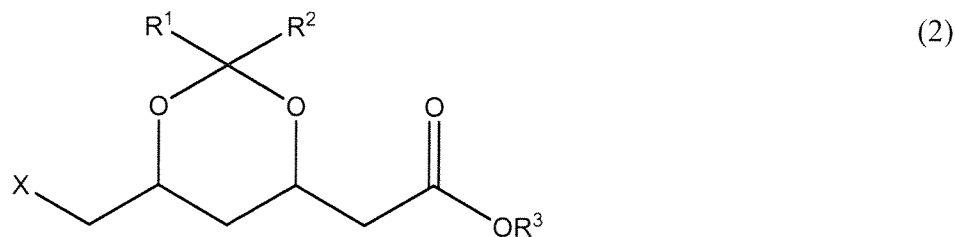
Claim 1. Process for the preparation of a 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivative according to formula 1,



wherein

**R<sup>1</sup>**, **R<sup>2</sup>** and **R<sup>3</sup>** are each independently a C1-4 alkyl group or wherein **R<sup>1</sup>** and **R<sup>2</sup>** together with the C-atom to which they are bound form a 5- or 6-membered cycloalkyl and **Y** stands for **R<sup>A</sup>**-CO- or for **R<sup>B</sup>**-SO<sub>2</sub>- where **R<sup>A</sup>**, **R<sup>B</sup>** are chosen from the group of alkyl or aryl with 1-12 C-atoms,

from its corresponding 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivative according to formula 2,



wherein

**R<sup>1</sup>**, **R<sup>2</sup>** and **R<sup>3</sup>** are as defined above and

**X** stands for a halogen, in the presence of a phase transfer catalyst and an oxylating agent, characterized in that a quarternary phosphonium ion according to formula 3,



wherein

**R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>** each independently stand for an alkyl, cycloalkyl, aralkyl or aryl with 1 to 12 C-atoms,

is used as a phase transfer catalyst and an ion according to formula 4,



wherein **Y** is as defined above,

is used as an oxylating agent.

Claim 2. Process according to claim 1, characterized in that **R<sup>A</sup>, R<sup>B</sup>** are chosen from the group of C<sub>1</sub>-C<sub>4</sub> alkyl or aryl with 6-10 C-atoms.

Claim 3. Process according to claim 1, characterized in that as a phase transfer catalyst a quarternary phosphonium salt according to formula 3a,



wherein

**R**<sup>4</sup>, **R**<sup>5</sup>, **R**<sup>6</sup> and **R**<sup>7</sup> are as defined above and

**A** stands for a halogen,

is used and in that an acid salt according to formula 4a,



wherein

**Y** is as defined above and

**M** stands for alkali metal or an alkaline metal,

is used as an oxylating agent.

Claim 4. Process according to claim 3, characterized in that the quarternary phosphonium salt according to formula 3a is used in a molar equivalent amount of 0.05 to 0.7 relative to the amount of compound according to formula 2.

Claim 5. Process according to claim 4, characterized in that the quarternary phosphonium salt according to formula 3a is used in a molar equivalent amount of 0.1 to 0.5 relative to the amount of compound according to formula 2.

Claim 6. Process according to any of claims 1-5, characterized in that the process is carried out at a temperature between 100 and 160° C.

Claim 7. Process according to any of claims 1-5, characterized in that the process is carried out at a temperature between 110 and 150° C.

Claim 8. Process according to any of claims 1-5, characterized in that the compound according to formula 1 is tert-butyl 2-{(4R,6S)-2,2 dimethyl-6-[(methyl-carbonyloxy)methyl]-1,3-dioxan-4-yl} acetate and in that the compound according to

formula 2 is tert-butyl 2-[(4R,6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxan-4yl]acetate.



**10. Evidence Appendix**

Supporting documents:

Exhibit A. Phase Transfer Catalysis, Principles and Techniques by C.M. Starks, Academic Press (1978) 140-147 (previously submitted in the response filed on August 20, 2007);

Exhibit B. U.S. Patent No. 5,594,153 (previously submitted in the response filed on August 20, 2007);

Exhibit C. Phase Transfer Catalysis Communications by Halpern, (1997) 3(1), 1, 2, 4 and 6-12 (previously submitted in the response filed on August 20, 2007);

Exhibit D. Tetrahedron Letters (1982) 23, 5407-5408 by Bram *et al.* (previously submitted in the response filed on August 20, 2007);

Exhibit E. Israel Journal of Chemistry (1985) 26, 291-298 by Bram *et al.* (previously submitted in the response filed on August 20, 2007).

**11.    Related Proceedings Appendix**

No information is appended under this section.

**Exhibit A**

# C.M. Starks, C.L. Liotta, "Phase Transfer Catalysis,"

140

## 4. Simple Displacement Reactions

Academic Press, 1978

TABLE 19  
Phase Transfer Catalyzed Reactions of  $\text{Na}_2\text{S}$  with Alkyl Halides  
in Yield Dielectric Solvents [74, 75]

| Alkyl halide                      | $\text{Na}_2\text{S}$<br>(mol eq) | Catalyst <sup>a</sup><br>(mol eq) | Temp.<br>(°C) | Time<br>(min)    | Yield of sulfide<br>(%) |
|-----------------------------------|-----------------------------------|-----------------------------------|---------------|------------------|-------------------------|
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 0.6                               | 0.1                               | 70            | 40               | 99.90 <sup>b</sup>      |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 2.5                               | 0.1                               | 70            | 40               | 99.91 <sup>c</sup>      |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 1.0                               | 0.1                               | 70            | 40               | 98 <sup>d</sup>         |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 0.6                               | 0.1                               | 70            | 40               | 98 <sup>e</sup>         |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 0.6                               | 0.05                              | 70            | 70               | 98 <sup>f</sup>         |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 0.6                               | 0.033                             | 70            | 120              | 98 <sup>g</sup>         |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 0.6                               | 0.025                             | 70            | 160              | 97 <sup>h</sup>         |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 0.6                               | 0.1                               | 70            | 10               | 100.94 <sup>i</sup>     |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 0.6                               | 0.1                               | 70            | 300              | 98.90 <sup>j</sup>      |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 0.6                               | 0.1                               | 110           | 120              | 99 <sup>k</sup>         |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 0.6                               | 0.1                               | 70            | 20               | 100.91 <sup>l</sup>     |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 0.6                               | 0.033                             | 70            | 70               | 98 <sup>m</sup>         |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 0.6                               | 0.1                               | 70            | 80               | 99.91 <sup>n</sup>      |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 0.6                               | 0.1                               | 70            | 500 <sup>o</sup> | 90.81 <sup>p</sup>      |
| $1-\text{C}_6\text{H}_5\text{Cl}$ | 7.0                               | 0.15 <sup>r</sup>                 | 100           | 24 hr            | 95 <sup>s</sup>         |

<sup>a</sup> Hexadecyltributylphosphonium bromide as catalyst.

<sup>b</sup> GLC analysis.

<sup>c</sup> Isolated yield.

<sup>d</sup> Reaction carried out under  $\text{N}_2$ .

<sup>e</sup> Resin beads of lightly cross-linked polystyrene-vinylbenzyl chloride. This run from Mitchell *et al.* [75].

<sup>f</sup> Catalyst was tetra-*n*-butylammonium bisulfate.

<sup>g</sup> Product was RSH rather than RSR.

**TYPICAL PROCEDURE:** *n*-Octyl Sulfide [74] Reprinted with permission from D. Landini and F. Rolla, *Synthesis*, p. 565 (1974). 1-Chlorooctane (14.9 g, 0.1 mol), sodium sulfide nonahydrate (14.4 g, 0.06 mol), hexadecyltributylphosphonium bromide (5.1 g, 0.01 mol), and water (30 ml) were mixed in a flask equipped with magnetic stirrer and reflux condenser, and heated at 70° (bath temperature) with vigorous stirring. The reaction was followed by G. L. C. (SE 30, 3% over Chromosorb at 125°). After 40 min (99% conversion) the organic layer was separated, washed with water, dried over calcium chloride and vacuum distilled to give *n*-octyl sulfide, yield: 11.6 g (91%); b.p. 160–162°/4 torr;  $n_D^{20} = 1.4690$ ....

By treating the distillation residue with light petroleum, 4.6 g (90%) of the phosphonium salt, m.p. 52–54°, were recovered. Small quantities of  $\text{C}^+$  product and catalyst can be obtained by extracting the aqueous phase with ethyl etc.

## V. Carboxylate Ion Displacements

It has long been known [76, 77] that aqueous solutions of sodium alkanoates react with alkyl halides in a second phase, provided an amine is

# principles and techniques

## V. Carboxylate Ion Displacements

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TABLE 20  
Comparison of Various Quaternary Ammonium Halides as  
Phase Transfer Catalysts for the Reaction of 1-Chlorobutane  
with Sodium Benzoate<sup>a</sup>

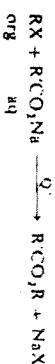
| Quaternary salt   | Yield of butyl benzoate<br>(%) |
|---|--------------------------------|
| $(\text{CH}_3)_4\text{N}^+\text{Br}^-$  | Trace                          |
| $\text{C}_6\text{H}_5\text{CH}_2(\text{CH}_2)_3\text{N}^+\text{Cl}^-$                         | 5.3                            |
| $\text{C}_{12}\text{H}_25\text{C}_6\text{H}_4\text{CH}_2(\text{CH}_2)_3\text{N}^+\text{Cl}^-$ | 56.7                           |
| $1-\text{C}_6\text{H}_5(\text{CH}_2)_3\text{N}^+\text{Br}^-$                                  | 72.3                           |
| $1-\text{C}_6\text{H}_5(\text{CH}_2)_3\text{N}^+\text{I}^-$                                   | 91.3                           |

<sup>a</sup> From Hennis *et al.* [86]. Reaction conditions: 1.5 moles sodium benzoate, 1.5 moles 1-chlorobutane, and 0.017 mole quaternary salt at 113°C for 2 hr

added as catalyst. Although a number of workers [78–85] have examined this two-phase reaction system in detail and postulated mechanisms to account for the catalytic activity of the amine, it remained for Hennis and co-workers [86, 87], to demonstrate that quaternary salts were formed in situ and that these functioned as phase transfer catalysts (Reaction 37). The

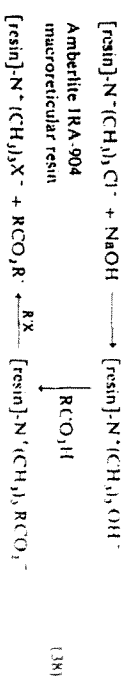


(37)



use of trialkylamines is particularly effective when benzyl chloride or other highly reactive RX is used, since these rapidly form quaternary salts. With quaternary salts as catalysts for the preparation of butyl benzoate, Hennis *et al.* [86] showed that the catalyst needs to have at least one moderately long alkyl group (Table 20) to function well. Benzyl-containing quaternary salts were rather ineffective for this reaction, presumably because of low thermal stability. Results for a number of carboxylate displacements are listed in Table 21 [61, 63, 77, 78, 86–98].


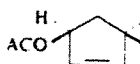
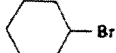
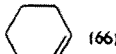
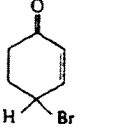
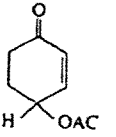
Cainelli and Manescalchi [99] have demonstrated that anion exchange resins may be used in a three-step procedure to prepare esters (Reaction 38).

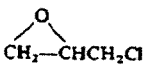
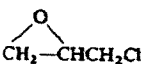
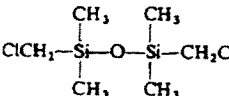
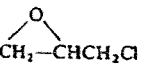


50–90% yields

This procedure, which corresponds to a resin-bound ion pair extraction technique, works best with alkyl iodides. Runs performed with catalytic

TABLE 21  
Phase Transfer Catalyzed Ester Syntheses

| Acid   | RX  | Catalyst   | Product (Yield, %)  | Ref.                     |
|--|---|--|---|--------------------------|
| CH <sub>3</sub> CO <sub>2</sub> H                | 1-C <sub>3</sub> H <sub>7</sub> Cl<br>(CH <sub>3</sub> ) <sub>3</sub> CCl         | Et <sub>3</sub> N<br>Et <sub>3</sub> N   | Ester (46)<br>No reaction   | 63<br>61                 |
|  |  | (C <sub>8</sub> H <sub>17</sub> ) <sub>3</sub> N <sup>+</sup> C <sub>3</sub> H <sub>7</sub> Br <sup>-</sup>  |  (75) | 88                       |
|  |  | Et <sub>3</sub> N  |  (66) | 61                       |
|  |  | (C <sub>8</sub> H <sub>17</sub> ) <sub>3</sub> N <sup>+</sup> C <sub>3</sub> H <sub>7</sub> Br <sup>-</sup>  |  (—)  | 88                       |
| C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl |   | Et <sub>3</sub> N, (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> P,<br>(n-C <sub>4</sub> H <sub>9</sub> ) <sub>3</sub> N, (n-C <sub>3</sub> H <sub>7</sub> ) <sub>3</sub> N<br>Et <sub>3</sub> N | Ester (93)<br>Ester (75)  | 63<br>61                 |
|  |   | Variety of crown ethers<br>Wide variety of amines  | Ester<br>Ester (> 90)   | 81<br>87, 77             |
|  | 1-C <sub>8</sub> H <sub>17</sub> Br<br>Myrcene hydrochloride                      | (C <sub>8</sub> H <sub>17</sub> ) <sub>3</sub> N <sup>+</sup> C <sub>3</sub> H <sub>7</sub> Br <sup>-</sup><br>Et <sub>3</sub> N<br>Et <sub>3</sub> N<br>Et <sub>3</sub> N                       | Ester (—)<br>Geranyl acetate (75–80)<br>α-Terpinyl acetate (8–10)                       | 88<br>89<br>90           |
|  | Bornyl chloride<br>Pinocaryyl chloride<br>Carvyl chloride                         | Et <sub>3</sub> N<br>Et <sub>3</sub> N<br>Et <sub>3</sub> N  | Linalyl acetate (8–10)<br>No reaction<br>No reaction<br>Carvyl acetate (90)             | 63<br>89<br>89<br>89, 90 |

|  |  |  |  |                            |
|--|--|--|--|----------------------------|
| CH <sub>3</sub> CH <sub>2</sub> CO <sub>2</sub> H                  | CH <sub>3</sub> Cl<br>CH <sub>2</sub> =CHCH <sub>2</sub> Cl<br>1-C <sub>6</sub> H <sub>9</sub> Cl  | Et <sub>3</sub> N<br>Et <sub>3</sub> N<br>Et <sub>3</sub> N  | Ester (96)<br>Ester (87)<br>Ester (80)   | 87<br>87<br>87             |
| CH <sub>2</sub> =CHCO <sub>2</sub> H                               | <br>C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Cl<br>p-C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Cl<br>C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> Cl<br>CH <sub>3</sub> Cl <sub>2</sub> | Quaternary phosphonium salts<br>C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> N <sup>+</sup> Me <sub>3</sub> Cl <sup>-</sup><br>C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> N <sup>+</sup> Et <sub>3</sub> Cl <sup>-</sup><br>C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> N <sup>+</sup> Et <sub>3</sub> Cl <sup>-</sup><br>(C <sub>4</sub> H <sub>9</sub> ) <sub>4</sub> N <sup>+</sup> HSO <sub>4</sub> <sup>-</sup> | Ester (—)<br>Ester (77)<br>Ester (—)<br>Ester (—)<br>(RCO <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> (79) | 91<br>92<br>92<br>92<br>93 |
| CH <sub>2</sub> =C(CH <sub>3</sub> )CO <sub>2</sub> H              |   | (CH <sub>3</sub> ) <sub>4</sub> N <sup>+</sup> Cl <sup>-</sup><br>Phosphonium salts  | Ester (91.3)<br>Ester (—)  | 94<br>91                   |
|  |   | Et <sub>3</sub> N  | Diester (45)   | 61                         |
| HO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H | CH <sub>2</sub> Cl <sub>2</sub>  | (C <sub>4</sub> H <sub>9</sub> ) <sub>4</sub> N <sup>+</sup> HSO <sub>4</sub> <sup>-</sup>   | No reaction  | 93                         |
| HO <sub>2</sub> C-C(=C)-CO <sub>2</sub> H<br>H H                   | 1-C <sub>10</sub> H <sub>21</sub> -Cl  | Et <sub>3</sub> N  | Diester (74)   | 78                         |
| (CH <sub>3</sub> ) <sub>3</sub> CCO <sub>2</sub> H                 | CH <sub>2</sub> Cl <sub>2</sub>  | (C <sub>4</sub> H <sub>9</sub> ) <sub>4</sub> N <sup>+</sup> HSO <sub>4</sub> <sup>-</sup>   | (RCO <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> (80)  | 93                         |
| HO <sub>2</sub> C(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> H |   | C <sub>12</sub> H <sub>25</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -N <sup>+</sup> (CH <sub>3</sub> ) <sub>2</sub> -CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> Cl <sup>-</sup>   | Resin  | 95                         |

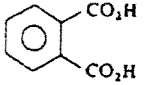

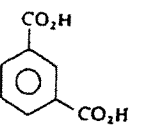
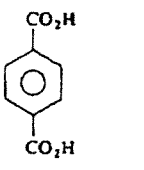



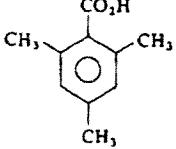
| Acid  | RX  | Catalyst                 | Product<br>(Yield, %) | Ref.   |
|---|---|--------------------------|-----------------------|--------|
| $C_6H_5CO_2H$   | $CH_2Cl$  | $Et_3N$                  | Ester (96)            | 87     |
|   | $CH_2Cl_2$  | $(C_4H_9)_4N^+ HSO_4^-$  | $(RCO_2)_2CH_2$ (88)  | 93     |
|   | $1-C_3H_7Cl$  | $Et_3S$ or $(C_6H_5)_3P$ | Ester (—)             | 96     |
|   | $2-C_3H_7Cl$  | $Et_3S$ or $(C_6H_5)_3P$ | Ester (—)             | 96     |
|   | $CH_2=CHCH_2Cl$   | $Et_3N$                  | Ester (93)            | 87     |
|   |   | $Et_3S$ or $(C_6H_5)_3P$ | Ester (—)             | 96, 86 |
|   | $1-C_4H_9Cl$  | $Et_3N$                  | Ester (85)            | 87     |
|   | $(CH_3)_3C-Br$  | $Et_3N$                  | Ester (12)            | 78     |
|   | $1-C_6H_{13}Cl$   | $Et_3N$                  | Ester (47)            | 61     |
|   | $C_6H_5CH_2Cl$  | $Et_3N$                  | Ester (79)            | 61     |
|   |   |                          | (89)                  | 87     |
|   |   |                          | Ester (84)            | 93     |
|   |   |                          | Ester (85)            | 93     |
| $p-ClC_6H_4CO_2H$   | $CH_2Cl_2$  | $(C_4H_9)_4N^+ HSO_4^-$  | Ester (98)            | 87     |
| $p-O_2NC_6H_4CO_2H$   | $CH_2Cl_2$  | $(C_4H_9)_4N^+ HSO_4^-$  | Ester (87)            | 87     |
| $o-HOC_6H_4CO_2H$   | $CH_3Cl$  | $Et_3N$                  | Ester (92)            | 87     |
|   | $CH_2=CHCH_2Cl$   | $Et_3N$                  |                       |        |
|   | $1-C_4H_9Cl$  | $Et_3N$                  |                       |        |
|    | $CH_2Cl_2$  | $(C_4H_9)_4N^+ HSO_4^-$  | No reaction           | 93     |
|   |    |                          |                       |        |
|    | $CH_2-CHCH_2Cl$   | $C_6H_5CH_2N^+Me_3 Cl^-$ | Diester (—)           | 97     |
|   |   |                          | Resin (—)             | 95     |
|   | $1-C_4H_9Cl$  | $Et_3N$                  | Ester (98)            | 78     |
|   |   |                          |                       |        |
|   | $1-C_{10}H_{21}Cl$  | $Et_3N$                  | Ester (87)            | 78     |
|   | $CH_2Cl_2$  | $(C_4H_9)_4N^+ HSO_4^-$  | Polymer               | 93     |
| $CH_3(CH_2)_7CO_2H$   |  | $C_6H_5CH_2N^+Me_3 Cl^-$ | Ester (—)             | 97, 98 |
| $HO_2C(CH_2)_7CO_2H$  |  | $C_6H_5CH_2N^+Me_3 Cl^-$ | Diester (—)           | 97, 98 |
| $p-CH_3COC_6H_4CO_2H$   | $CH_2Cl_2$  | $(C_4H_9)_4N^+ HSO_4^-$  | $(RCO_2)_2CH_2$ (85)  | 93     |
| $CH_3(CH_2)_9CO_2H$   | $1-C_{12}H_{25}Cl$  | $Et_3N$                  | Ester (82)            | 78     |
| $HO_2C(CH_2)_8CO_2H$  |  | $C_6H_5CH_2NMe_3^+ Cl^-$ | Diester (—)           | 97, 98 |
|  | $CH_2Cl_2$  | $(C_4H_9)_4N^+ HSO_4^-$  | $(RCO_2)_2CH_2$ (87)  | 78     |

TABLE 21 (continued)

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| Acid   | RX                                    | Catalyst   | Product<br>(Yield, %)                            | Ref. |
|--|---------------------------------------|--|--|------|
|  | CH <sub>2</sub> Cl <sub>2</sub>       | Et <sub>3</sub> N  | (RCO <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> | 78   |
|  | ClCH <sub>2</sub> CH <sub>2</sub> Cl  | Et <sub>3</sub> N  |  | 78   |
|  | 1-C <sub>6</sub> H <sub>5</sub> Cl    | Et <sub>3</sub> N  |  | 78   |
|  | 1-C <sub>8</sub> H <sub>17</sub> Cl   | Et <sub>3</sub> N  |  | 78   |
|  | 2-C <sub>8</sub> H <sub>17</sub> Cl   | Et <sub>3</sub> N  |  | 78   |
| Ampicillin   | Alkylating agents<br>                 | Quaternary salts<br>or crown ethers  | Penicillin esters                                | 98a  |
| CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub> CO <sub>2</sub> H | CH <sub>2</sub> =CHCH <sub>2</sub> Cl | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> N <sup>+</sup> (CH <sub>3</sub> ) <sub>3</sub> Cl <sup>-</sup> | Ester (—)  | 98   |

### V. Carboxylate Ion Displacements

amounts of resin did not give satisfactory results. Starks [16], using the general procedure described next, obtained 95–98% yields of a variety of esters from simple alkyl halides and sodium carboxylates.

**Preparation:** *1-Decyl Acetate* [16] A mixture of 55 g (0.25 mole) of 1-bromodecane, 270 g (2.0 moles) of sodium acetate trihydrate, and 10 g of (C<sub>10</sub>H<sub>21</sub>)<sub>2</sub>CH<sub>2</sub>N<sup>+</sup>Cl<sup>-</sup> was heated to 105°C with good stirring for 1 h. Water (350 ml) was added. The organic layer was separated and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. 1-Decyl acetate in 97% yield was recovered from the quaternary salt catalyst by distillation through a wiped-film, short-path evaporator at 100°C and 0.1 Torr.

The water of hydration in NaOAc·3H<sub>2</sub>O is sufficient to form a liquid aqueous phase at 105°C so no water was added in this run. The large excess of sodium acetate used is necessary to overcome the unfavorable preference of quaternary cation for bromide over acetate ( $K_p \approx 0.05 \text{ AcO}^-/\text{Br}^-$ ). Greater efficiency in acetate use can be realized by using a lower sodium acetate: alkyl halide mole ratio (~1:1) with three or four replacement steps of the aqueous phase by fresh sodium acetate. With larger carboxylate ions (propionate, butyrate, pentanoate, etc.) the anion partitioning ratio becomes increasingly more favorable, so that with acids larger than hexanoic, only one step with about 2 moles of sodium alkanoate per mole of alkyl halide is required for essentially complete conversion.

Brändström [3] has demonstrated that high yields (>90%) of esters may similarly be obtained by the ion pair extraction technique. This technique may also be used to prepare methylene esters in 60–to 90% yields from carboxylic acids and dichloromethane (Reaction 39).



The poor nucleophilicity of acetate ion toward various substrates in condensed systems has been attributed to a combination of polarizability, basicity, and solvation factors. Liotta *et al.* [29] reported that acetate solubilized as the potassium salt in acetonitrile or benzene containing 18-crown-6 became sufficiently nucleophilic to react smoothly and quantitatively, even at room temperature, with a wide variety of organic substrates under L.S.-PTC conditions. Displacement reactions at 1°, 2°, 3°, and benzylic positions, along with competing elimination processes, have been demonstrated with this reagent, which has been termed "bare" acetate. The data summarized in Table 22 [100] deal specifically with the solvent acetonitrile. The same products were obtained in benzene but the reaction rates were slower. In the absence of crown, little or no reaction took place under identical conditions covering the same periods of time. For instance, in the case of benzyl bromide (run 1, Table 22), the most reactive substrate reported in Table 22, less than 5% benzyl acetate was formed after several days with

**Exhibit B**





US005594153A

**United States Patent** [19][11] **Patent Number:** **5,594,153****Thottathil et al.**[45] **Date of Patent:** **Jan. 14, 1997**

[54] **PROCESS FOR THE PREPARATION OF  
1,3-DIOXANE DERIVATIVES USEFUL IN  
THE PREPARATION OF HMG-COA  
REDUCTASE INHIBITORS**

0374922 6/1990 European Pat. Off. .

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[21] Appl. No.: **498,493**

[22] Filed: **Jul. 5, 1995**

**Related U.S. Application Data**

[62] Division of Ser. No. 135,604, Oct. 8, 1993, Pat. No. 5,457,  
227, which is a division of Ser. No. 858,907, Mar. 27, 1992,  
Pat. No. 5,278,313.

[51] Int. Cl.<sup>6</sup> ..... **C07D 319/06**

[52] U.S. Cl. .... **549/374; 549/375**

[58] Field of Search ..... **549/374, 375**

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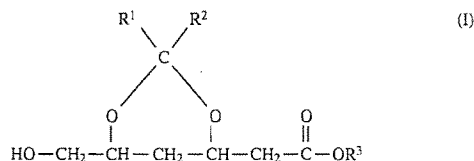
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*Primary Examiner*—David B. Springer

*Attorney, Agent, or Firm*—Burton Rodney

[57] **ABSTRACT**

A novel, overall process for the preparation of a compound of the formula I:



where

R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen, an alkyl group, a cycloalkyl group, an aryl group or, taken together with the carbon atom to which they are attached, form a cycloalkyl group; and

R<sup>3</sup> is hydrogen, an alkyl group, or an aryl group, or salts thereof, useful as intermediates in the preparation of HMG-CoA reductase inhibitors; novel methods within the overall process; and novel intermediates produced by those methods.

**11 Claims, No Drawings**

## 1

**PROCESS FOR THE PREPARATION OF  
1,3-DIOXANE DERIVATIVES USEFUL IN  
THE PREPARATION OF HMG-COA  
REDUCTASE INHIBITORS**

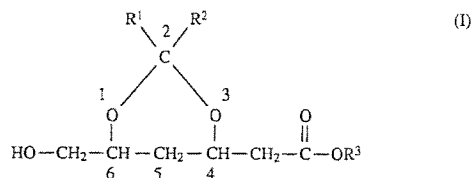
This is a division of application Ser. No. 08/135,604, filed Oct. 8, 1993, U.S. Pat. No. 5,457,227 which is a division of application Ser. No. 07/585,907, filed Mar. 27, 1992, U.S. Pat. No. 5,278,313.

**FIELD OF THE INVENTION**

The present invention relates to a process for the preparation of 1,3-dioxane derivatives useful in the preparation of HMG-CoA reductase inhibiting compounds. The instant invention also relates to the novel intermediates produced.

**SUMMARY OF THE INVENTION**

The instant invention provides a process for the preparation of compounds of the formula I:



where

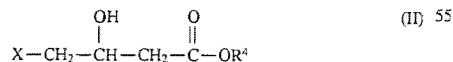
R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen, an alkyl group, a cycloalkyl group, an aryl group or, taken together with the carbon atom to which they are attached, form a cycloalkyl group; and

R<sup>3</sup> is hydrogen, an alkyl group or an aryl group; and salts thereof, and especially for the preparation of optically active such compounds.

Compounds of the formula I are useful as intermediates in the preparation of inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which inhibitors are useful, for example, in the treatment of hypercholesterolemia, hyperlipoproteinemia, hyperlipidemia and atherosclerosis. The instant invention provides a convenient process for the preparation of compounds of the formula I in good yields, particularly for the preparation of chiral compounds of the formula I having the 4R,6S configuration which are preferred in the preparation of HMG-CoA reductase inhibitors.

The process of the instant invention comprises the steps of:

(a) condensing a compound of the formula II:



where

X is a halogen atom; and

R<sup>4</sup> is an alkyl group, a cycloalkyl group or an aryl group,

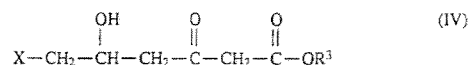
with a compound of the formula III, or a salt thereof:



where

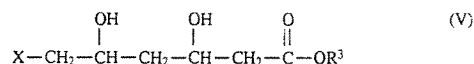
## 2

R<sup>3</sup> is as defined above for the formula I; in the presence of a condensation agent, to form a compound of the formula IV, or a salt thereof:



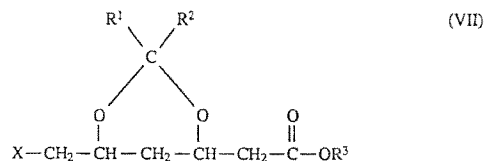
where X is as defined in formula II and R<sup>3</sup> is as defined in formula I;

(b) reducing, in the presence of a reducing agent, the compound of the formula IV or salt thereof prepared in step (a) to form a compound of the formula V, or a salt thereof:



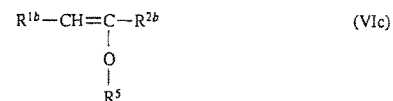
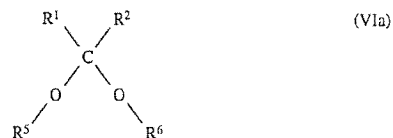
where X is as defined in formula II and R<sup>3</sup> is as defined in formula I;

(c) preparing a compound of the formula VII, or a salt thereof:



where

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined in formula I; and X is as defined in formula II, by reacting the compound of formula V or salt thereof prepared in step (b) with a compound of the formula VIa, VIb or VIc:



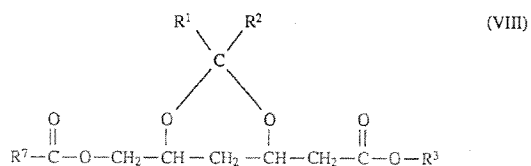
where

R<sup>1</sup> and R<sup>2</sup> are as defined in the formula I;

R<sup>1b</sup> and R<sup>2b</sup> are each independently hydrogen, an alkyl group, a cycloalkyl group, an aryl group or, taken together with the carbon atoms to which they are attached, form a 1,2-cycloalkenyl group; and

R<sup>5</sup> and R<sup>6</sup> are each independently an alkyl group, in the presence of an acidic condensation agent;

(d) preparing a compound of the formula VIII, or a salt thereof:



where

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined in formula I; and

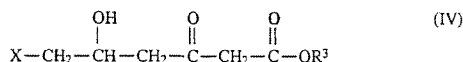
3

- $R^7$  an alkyl group or an aryl group, by displacing the group X of the compound of the formula VII or salt thereof prepared in step (c) with an acyloxy group of the formula  $-\text{O}-\text{C}(\text{O})-\text{R}^7$  by use of a displacement agent; and
- (e) hydrolyzing the compound of the formula VIII or salt thereof prepared in step (d) to produce the compound of the formula I or a salt thereof.

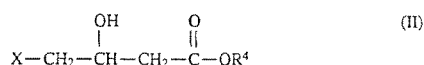
#### DETAILED DESCRIPTION OF THE INVENTION

The instant invention provides a novel, overall process for the preparation of compounds of the formula I or salts thereof comprising the steps (a) through (e) set forth above. In addition, the instant invention provides the individual methods of each of steps (a) through (e) which are novel methods, and the novel intermediates of the formulae IV, V, VII and VIII or salts thereof formed therein, as described following. In the following description, reference to a compound of a designated formula includes compounds of that structure or salts thereof unless otherwise specified. As used in this specification, reference to a compound of a designated formula or salt thereof is defined to include solvates, such as hydrates, of said compound or salt.

In step (a), a compound of the formula IV:



is prepared by a method wherein a compound of the formula II:



is condensed with a compound of the formula III:



in the presence of a condensation agent. In the formulae II, III and IV,  $R^3$  is preferably a lower alkyl group such as t-butyl,  $R^4$  is preferably a lower alkyl group such as methyl or ethyl, and X is preferably a bromine or, particularly, a chlorine atom.

The starting materials of the formulae II and III of the method of step (a) may be prepared by one of ordinary skill in the art. For example, the compounds of the formula II may be prepared by a method such as that described in U.S. application Ser. No. 07/693,893, filed May 1, 1991 by Patel et al., incorporated herein by reference. The compounds of the formula III are readily available commercial products and/or may be prepared by methods well known to one of ordinary skill in the art.

Any compound effecting the reaction of step (a) may be employed as the condensation agent. Basic condensation agents are preferred. It is particularly preferred to employ a basic metallic condensation agent such as  $\text{NaNH}_2$ , potassium hexamethyldisilazide (KHMDs),  $\text{KNH}_2$ , a lithium amide compound such as lithium diisopropylamide (LDA) or lithium dicyclohexylamide (LiDCYA), or any other such bases. Lithium hexamethyldisilazide (LiHMDS) is particularly preferred.

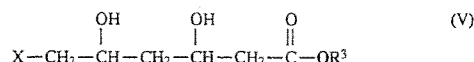
The method of step (a) is preferably conducted at a temperature of from about  $25^\circ\text{C}$ . to about  $-90^\circ\text{C}$ ., most preferably from about  $-40^\circ\text{C}$ . to about  $-78^\circ\text{C}$ . The reaction of step (a) is preferably conducted under an inert atmosphere such as nitrogen or argon.

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It is preferred to employ amounts of starting materials such that the molar ratio of the compound of the formula III to the compound of the formula II is from about 8:1 to about 3:1, most preferably from about 4:1 to about 3.5:1; and the molar ratio of the condensation agent to the compound of the formula II is from about 8:1 to about 3:1, most preferably from about 4:1 to about 3.5:1. Solvents are preferably employed which are selected from organic solvents such as ether, hexanes, dioxane, toluene, cyclohexane, or any other inert organic solvent. The organic solvent is most preferably tetrahydrofuran.

The method of step (a), and compounds of the formula IV, are novel.

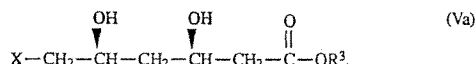
In the method of step (b), a compound of the formula V:



is prepared by reducing the compound of the formula IV prepared in step (a) above by use of a reducing agent.

Any reducing agent effecting the reaction of step (b) may be employed. Exemplary reducing agents include sodium borohydride, zinc borohydride, lithium borohydride, diisobutylaluminum hydride, sodium bis(2-methoxyethoxy)aluminum hydride or similar hydride reducing agents and agents effecting catalytic hydrogenation such as hydrogen/catalyst combinations where the catalyst is, for example, Raney nickel, platinum, rhodium, palladium or palladium hydroxide ( $\text{Pd}(\text{OH})_2$ ), any of which may be employed alone, in oxide form (for example,  $\text{PtO}_2$ ), or on a carbon support (for example, Pd on carbon, Pt on carbon,  $\text{PtO}_2$  on carbon or  $\text{Pd}(\text{OH})_2$  on carbon).

It is preferred, in step (b), to prepare a compound of the formula V having the preferred stereoisomeric configuration of formula Va:



Stereospecificity of the reduction reaction may be achieved by the use of a hydride reducing agent. Particularly high stereospecificity may be achieved by the use of a combination of sodium borohydride and a trialkylborane or alkylalkoxyborane such as an alkoxydialkylborane. The reducing agent employed is most preferably a mixture of a trialkylborane such as triethylborane or an alkoxydialkylborane such as methoxydiethylborane, and sodium borohydride.

The stereospecific reduction is preferably carried out by sequential addition of borane reagent followed by sodium borohydride. At the end of the reduction, the formed boron complex may be hydrolyzed by a peroxide such as hydrogen peroxide in the presence of a base such as sodium hydroxide to obtain compounds of the formula Va.

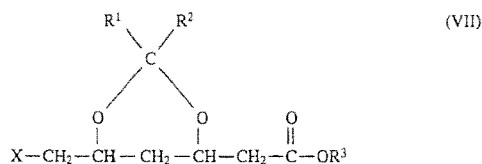
The method of step (b) is preferably conducted at a temperature of from about  $-30^\circ\text{C}$ . to about  $-90^\circ\text{C}$ ., most preferably from about  $-60^\circ\text{C}$ . to about  $-80^\circ\text{C}$ . The reaction of step (b) is preferably conducted under an inert atmosphere such as nitrogen or argon.

Molar ratios of reducing agent to the starting compound of the formula IV are preferably from about 1:1 to about 4:1, particularly those from about 2:1 to about 4:3. Solvents are preferably employed which are selected from inert organic solvents such as tetrahydrofuran, ether, dioxane and the like, in combination with an alcoholic solvent such as methanol, ethanol and the like, most preferably a mixture of tetrahydrofuran and methanol.

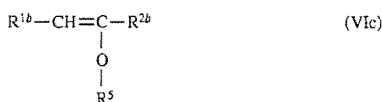
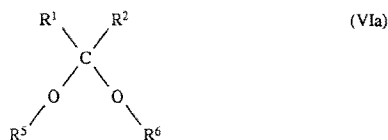
The method of step (b), and the compounds of the formula V, are novel.

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In the method of step (c), a compound of the formula VII:



is prepared by reacting the compound of the formula V prepared in step (b) above with a compound of the formula VIa, VIb or VIc:



in the presence of an acidic condensation agent.

In the above formulae,  $\text{R}^1$  and  $\text{R}^2$  are preferably a lower alkyl group such as methyl,  $\text{R}^{1b}$  is preferably hydrogen and  $\text{R}^{2b}$  is preferably a lower alkyl group such as methyl, and  $\text{R}^5$  and  $\text{R}^6$  are preferably the same or different lower alkyl group, such as methyl or ethyl.  $\text{R}^5$  and  $\text{R}^6$  are most preferably both methyl. The starting compounds of the formulae VIa, VIb and VIc are readily available, or may be prepared by methods well known to the skilled artisan.

Any organic or mineral acid which effects the reaction of step (c) may be employed as the condensation agent. Exemplary acidic condensation agents include acidic polymeric resins, p-toluenesulfonic acid, methanesulfonic acid, pyridinium p-toluene sulfonate, hydrochloric and sulfuric acids, cupric sulfate, cupric bromide and the like and, particularly, camphorsulfonic acid (CSA). When water is formed in the condensation reaction of step (c) distillation, or a drying agent or molecular sieve, may be employed to facilitate removal thereof.

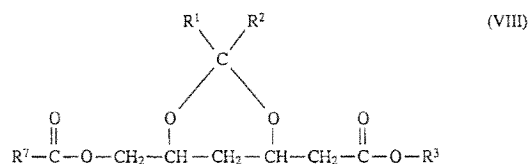
The method of step (c) is preferably conducted at a temperature of from about  $0^\circ\text{C}$ . to about  $60^\circ\text{C}$ ., most preferably from about  $10^\circ\text{C}$ . to about  $30^\circ\text{C}$ . The reaction of step (c) is preferably conducted under an inert atmosphere such as nitrogen or argon.

Molar ratios of the starting materials are preferably selected so that the molar ratio of the compound of the formula VIa, VIb or VIc employed to the compound of the formula V is from about 1:1 to about 20:1, most preferably from about 3:1 to about 5:1. The molar ratio of acidic condensation agent to the compound of the formula V is preferably from about 1:1 to about 0.001:1, most preferably from about 0.01:1 to about 0.05:1. The reaction of step (c) is preferably conducted without the addition of solvent, although solvents such as toluene, chloroform and the like, preferably dichloromethane, may be employed.

The method of step (c) and the compounds of the formula VII, are novel.

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In the method of step (d), a compound of the formula VIII:



is prepared by displacing the group X of the compound of the formula VII prepared in step (c) above with an acyloxy group of the formula  $-\text{O}-\text{C}(\text{O})-\text{R}^7$  by use of a displacement agent.

Any displacement agent effecting the reaction of step (d) may be employed. Exemplary acyloxy displacement agents are those of the formula IX:



where  $\text{R}^7$  is as defined in the formula VIII and M is a metal, preferably an alkali metal, such as sodium, cesium or potassium; or an ammonium group, such as an alkyl ammonium group. The compounds of formula IX are known and may be prepared by methods known to the skilled artisan. It is particularly preferred to employ displacement agents having the formula IXa:



where  $\text{R}^7$  is as defined in the formula VIII and  $\text{R}^8$  is an alkyl group, preferably a lower alkyl group such as n-butyl.

The method of step (d) is preferably conducted at a temperature of from about  $0^\circ\text{C}$ . to about  $130^\circ\text{C}$ ., most preferably from about  $50^\circ\text{C}$ . to about  $120^\circ\text{C}$ . The reaction of step (d) is preferably conducted under an atmosphere of inert gas such as argon.

Molar ratios of the starting materials are preferably selected so that the molar ratio of the compound of the formula IX or IXa to the compound of the formula VII is from about 1:1 to about 5:1, most preferably from about 2:1 to about 3:1. Solvents are preferably employed which are selected from inert organic solvents, such as dimethylformamide, acetonitrile, dimethylsulfoxide, or dimethylacetamide, most preferably N-methylpyrrolidinone.

The method of step (d) is novel. Further, compounds of the formula VIII where  $\text{R}^7$  is an alkyl group are novel, and are preferably prepared by the instant method. Use of compounds of the formula VIII having as  $\text{R}^7$  an alkyl group, most preferably a lower alkyl group such as methyl, facilitates the hydrolysis procedure of step (e) described below. In particular, the by-products formed by the use of such compounds in step (e), such as methyl acetate or acetic acid, are volatile and are readily separated from the desired compound of the formula I relative to the by-products formed when a compound of the formula VIII where  $\text{R}^7$  is aryl is employed.

In the method of step (e), a compound of the formula I is prepared by hydrolyzing the compound of the formula VIII prepared in step (d) above. Any hydrolyzing agent effecting the reaction of step (e) may be employed. Exemplary hydrolyzing agents are basic compounds such as alkali metal hydroxides (for example, sodium hydroxide, potassium hydroxide or lithium hydroxide), or any other hydroxide base. Potassium carbonate is particularly preferred as the hydrolyzing agent. The molar ratio of hydrolyzing agent to the compound of the formula VIII is preferably from about 2:1 to about 1:2, most preferably from about 1:1 to about 1:2.

Use of a mildly basic medium is particularly advantageous in step (e). A "mildly basic medium", as used in this specification, denotes a reaction medium at a pH which selectively hydrolyzes the  $R^7-C(O)-O$ -ester group of the compound of the formula VIII, relative to hydrolysis of the  $R^3-O-C(O)$ -ester group. Preferably, a pH of from about 7 to about 12, most preferably from about 8 to 10, is employed. It is particularly desirable to employ a medium such that substantially all of the product formed in step (e) is the compound of the formula I, for example, an amount greater than about 99% of the product formed.

It is further preferred to employ a mild base to achieve the mildly basic medium described above. As used in this specification, a "mild base" is a base having a pKa of from about 5 to about 12, most preferably from about 6 to about 10. Exemplary mild bases include alkali metal carbonates such as sodium carbonate, and particularly potassium carbonate as discussed above. pKa may be determined by the method described in Cookson, Chem. Rev., 74, 5-28 (1974).

In addition to allowing selective hydrolysis, use of a mild base and mildly basic medium is advantageous in avoiding instability of the compound of formula I, for example, elimination of the group  $-O-C(R^1)(R^2)-O-$  (ring opening), which may occur under strongly basic conditions.

The method of step (e) is preferably conducted at a temperature of from about 0° C. to about 100° C., most preferably from about 10° C. to about 40° C. Alcoholic solvents are preferably employed, exemplified by alkanols such as methanol.

The method of step (e) is novel where (i) a mild base or mildly basic medium is employed and/or (ii) a compound of the formula VIII is employed where  $R^7$  is an alkyl group. Use of a compound of the formula VIII where  $R^7$  is an alkyl group is particularly advantageous for the reasons described above.

Exemplary compounds falling within the scope of the present invention include:

(S)-6-chloro-5-hydroxy-3-oxohexanoic acid, 1,1-dimethylethyl ester (formula IV);

(S)-6-bromo-5-hydroxy-3-oxohexanoic acid, 1,1-dimethylethyl ester (formula IV);

(R,S)-6-chloro-3,5-dihydroxyhexanoic acid, 1,1-dimethylethyl ester (formula V);

(R,S)-6-bromo-3,5-dihydroxyhexanoic acid, 1,1-dimethylethyl ester (formula V);

(4R-cis)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester (formula VII);

(4R-cis)-6-(bromomethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester (formula VII);

(4R-cis)-6-[(acetyloxy)methyl]-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester (formula VIII);

(4R-cis)-6-[(benzoyloxy)methyl]-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester (formula VIII); and

(4R-cis)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester (formula I).

In each of the above steps (a) through (e), solvates, as well as the salt or free form of the compounds, may be employed as starting materials or prepared as products. Solvates may be organic solvates or, preferably, hydrates. Salts include acidic or basic salts with inorganic or organic acids or bases. Exemplary salts include salts formed with nontoxic cations such as alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example, calcium or magnesium) cations or ammonium salts formed with non-

toxic amines such as trialkylamines, dibenzylamine, pyridine, N-methylmorpholine, N-methylpiperidine and the like.

The term "alkyl", as used in this specification, preferably denotes a straight or branched saturated carbon chain having from 1 to 21 carbon atoms. Exemplary alkyl groups include methyl, ethyl, i-propyl, n-propyl, t-butyl and n-butyl.

The term "lower alkyl", as used in this specification, preferably denotes an alkyl group as described above having from 1 to 8, most preferably 1 to 6, carbon atoms.

The term "cycloalkyl", as used in this specification, preferably denotes a saturated carbocyclic ring system having from 1 to 3 rings and from 3 to 21 carbon atoms. Exemplary cycloalkyl groups include cyclopentyl, cyclohexyl and cycloheptyl.

The term "cycloalkenyl", as used in this specification, preferably denotes a partially unsaturated carbocyclic ring system having from 1 to 3 rings and from 3 to 21 carbon atoms. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl and cycloheptenyl.

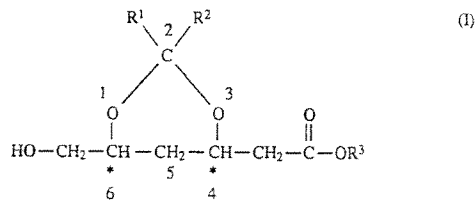
The term "aryl", as used in this specification, preferably denotes an unsaturated monocyclic or bicyclic carbocyclic ring system having from 6 to 12 carbon atoms. Exemplary aryl groups include phenyl, biphenyl and naphthyl.

Each of the alkyl (including lower alkyl), cycloalkyl, cycloalkenyl or aryl groups described above may optionally be substituted. Appropriate substituents include those groups allowing preparation according to the methods of the present invention. For example, the cycloalkyl, cycloalkenyl or aryl groups described above may be substituted by one or more alkyl groups.

The term "halogen", as used in this specification, denotes fluorine, iodine or preferably, bromine or chlorine.

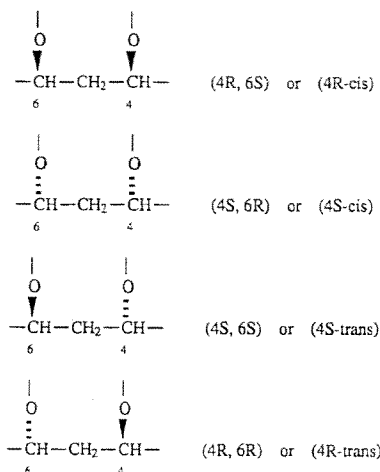
The present invention contemplates preparation of any of the compounds herein which may be in the form of mixtures of stereoisomers (e.g. racemates), mixtures of selected stereoisomers, and individual stereoisomers substantially free of other isomers. Mixtures of isomers may be separated into individual isomers according to methods which are known to the skilled artisan, for example, by fractional crystallization, fractional distillation, adsorption chromatography or other suitable separation processes. Resulting racemates may be separated into antipodes by introduction of suitable salt-forming groupings, e.g. by forming a mixture of diastereoisomeric salts with optically active salt-forming agents, separating the mixture into diastereoisomeric salts and converting the separated salts into the free compounds. The enantiomeric forms may also be separated by fractionation through chiral high pressure liquid chromatography columns. Most preferably, chiral compounds may be prepared directly by the selective stereoisomeric methods for preparation provided by the instant invention and described above.

In the preparation of inhibitors of HMG-CoA reductase having a preferred stereoisomeric configuration, it is desirable to employ chiral intermediates. In this regard, the compounds of formula I contain two asymmetric carbon atoms indicated by an asterisk as follows:

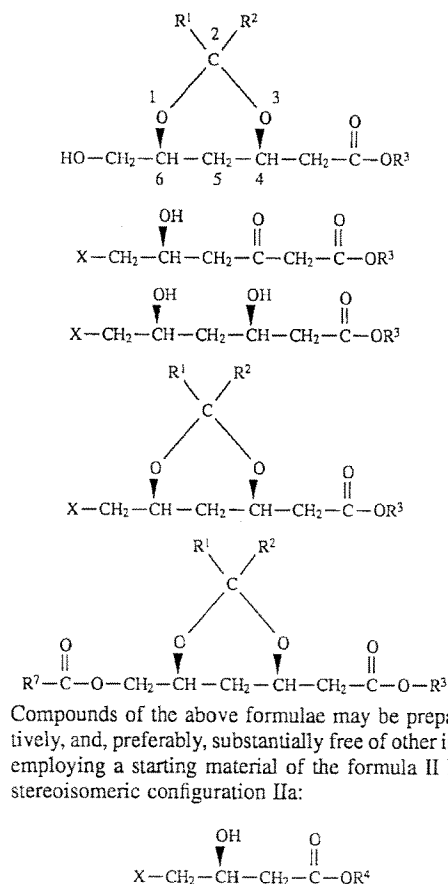


The compounds of the formulae V, VII and VIII also contain the above asymmetric carbon atoms at the analogous posi-

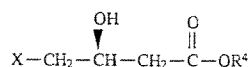
tions. The four stereoisomers resulting from the above asymmetric carbon atoms in the compounds of the formula I are designated as follows:



Compounds having the (4R-cis), that is, the following stereoisomeric configurations, are preferably prepared by the methods of the instant invention:



Compounds of the above formulae may be prepared selectively, and, preferably, substantially free of other isomers, by employing a starting material of the formula II having the stereoisomeric configuration IIa:

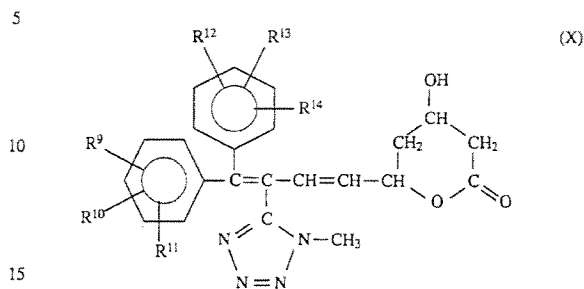


and by employing the stereoselective methods of steps (a) through (e) described above.

The compounds of the formula I prepared as described herein may be employed in the preparation of inhibitors of the enzyme HMG-CoA reductase. Exemplary such inhibi-

tors, and methods of preparation thereof, are described in U.S. Pat. No. 4,898,950, incorporated herein by reference.

It is particularly preferred to prepare HMG-CoA reductase inhibitors of the formula X:



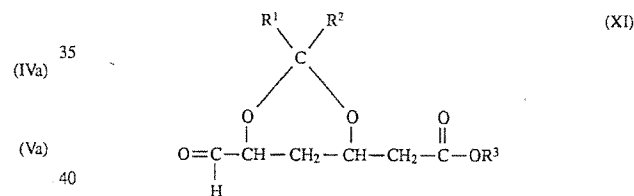
where

$\text{R}^9$  and  $\text{R}^{12}$  are each independently hydrogen, halogen,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkoxy or trifluoromethyl (preferably, where both  $\text{R}^9$  and  $\text{R}^{12}$  are fluorine); and

$\text{R}^{10}$ ,  $\text{R}^{11}$ ,  $\text{R}^{13}$  and  $\text{R}^{14}$  are each independently hydrogen, halogen,  $\text{C}_{1-4}$  alkyl or  $\text{C}_{1-4}$  alkoxy (preferably where all are hydrogen);

or salts thereof, which compounds are described in U.S. Pat. No. 4,898,950.

For example, a compound of the formula I or a salt thereof may be oxidized according to known methods, such as those described in A. J. Mancuso, S.-L. Huang and D. Swern, J. Org. Chem., 43, No. 12, 2480-2482 (1978), by use of a Swern oxidation reaction (oxalyl chloride in dimethylsulfoxide, with the addition of triethylamine) to yield a compound of the formula XI, or a salt thereof:



wherein  $\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$  are as defined in the formula I, and the latter compound employed in the preparation of a compound of the formula X or a salt thereof according to the methods described in the aforementioned U.S. Pat. No. 4,898,950.

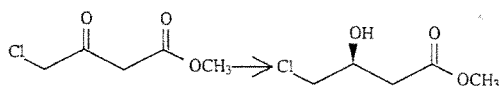
The following examples are provided to further illustrate the instant invention, and should not be construed as limiting the scope of the instant claims.

#### EXAMPLE 1

Preparation of  
(4R-cis)-6-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid,

1,1-dimethylethyl ester

(a) (S)-4-Chloro-3-hydroxybutanoic acid methyl ester

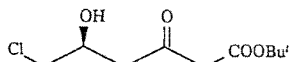


4-Chloro-3-oxobutanoic acid methyl ester was converted to the title compound according to the fermentation procedures described in U.S. patent application Ser. No. 07/693,893, filed May 1, 1991 by Patel et al.

The filtered fermentation batch (390 L, 1193.0 g by BPD) of the chlorohydrin so prepared was extracted with 570 L (2x) of ethyl acetate, and the phases were separated, concentrated and distilled yielding 1079 g (90.4%) of the crude title product (b.p. 50°–100° C./3–5 mmHg). The weight of the residue was 417 g. The crude product was fractionated in the laboratory on a 2.5x25 cm helix-filled column.

| Fractions                      |         |
|--------------------------------|---------|
| 1. b.p. 80–90° C./4.0–4.5 mmHg | 47.0 g  |
| 2. b.p. 90–93° C./4.0–3.5 mmHg | 843.3 g |
| 3. residue:                    | 94.7 g  |
| Total                          | 985.0 g |
| Title Product (fraction 2)     | 843.0 g |
| 78.1% yield (from crude)       |         |
| 70.7% recovery from the broth  |         |

(b) (S)-6-Chloro-5-hydroxy-3-oxohexanoic acid, 1,1-dimethylethyl ester

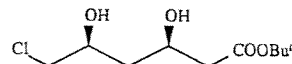


A flame-dried 5 L three-necked round bottomed flask was charged with tetrahydrofuran (THF) (distilled, 500 ml) and lithium hexamethyl-disilazide (1.715 L, 3.5 eq, 1M solution in THF) at –78° C. The THF was added to prevent the LiHMDS from precipitation. To this light brown solution was slowly added tert-butyl acetate (CH<sub>3</sub>CO<sub>2</sub>Bu<sup>t</sup>) (266 ml, 4.0 eq) over a period of 10 minutes at –78° C. At the end of the addition, the solution was stirred for another 40 minutes at –78° C.

To this light brown homogeneous reaction mixture was added a solution of (S)-4-chloro-3-hydroxybutanoic acid methyl ester, prepared in step (a) above and employed without further purification (75 g, 0.493 mole), in 60 ml THF over a period of 15 minutes. The addition was slightly exothermic. The internal temperature climbed from –78° C. to –74° C. during the addition.

The reaction was stirred at –78° C. for 1 hour, then at –50° C. for 1 hour. At this point thin-layer chromatography (TLC) indicated complete reaction (TLC: silica gel; Ethyl acetate (EtOAc):Hexane; 1:1; R<sub>f</sub>=0.56, UV visualization for title compound; R<sub>f</sub>=0.55, PMA visualization for starting material, (S)-4-chloro-3-hydroxybutanoic acid methyl ester). The reaction was quenched by the slow addition of acetic acid (AcOH) (200 ml) with vigorous stirring over a period of 30–40 minutes. The reaction mixture became heterogeneous due to the freezing of acetic acid. During the quench, the internal temperature was maintained between –50° C. and –40° C. The cooling bath was removed and the reaction was slowly allowed to warm to 0° C. The resulting thick yellow solution was poured into a mixture of ethyl acetate (EtOAc) (1 L) and H<sub>2</sub>O (deionized, 1L) in a separatory funnel. The aqueous layer was separated and extracted with EtOAc (300 mlx2). The combined EtOAc layer was washed with 1N HCl (500 mlx2), and half-saturated NaCl (500 mlx1). The combined HCl and NaCl washings were extracted with EtOAc (300 mlx1). All of the EtOAc extracts were then combined and washed with saturated NaHCO<sub>3</sub> (500 mlx2), half-saturated NaCl (500 mlx1) and brine (500 mlx2), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give 136.74 g of the title compound as a brown oil (approximately 100%). H-NMR indicated that no starting material remained. The product was approximately 90% pure by H-NMR, and TLC (the same conditions as previously described) showed a

major spot and two minor impurities (<5%). The product was used for the next step without any further purification. (c) (R,S)-6-Chloro-3,5-dihydroxyhexanoic acid, 1,1-dimethylethyl ester



The crude hydroxyketone (S)-6-chloro-5-hydroxy-3-oxohexanoic acid, 1,1-dimethylethyl ester (66.0 g) obtained in step (b) above was dissolved in THF (1.25 L) and HPLC grade methanol (MeOH) (630 ml) at –78° C. To this brown solution was added methoxydiethylborane (Et<sub>2</sub>BOMe) (285 ml, 1M solution in THF) over a period of 20 minutes. The addition was slightly exothermic and the solution became cloudy. At the end of the addition, the reaction solution was stirred for an additional 20 minutes. To this cloudy solution was added solid NaBH<sub>4</sub> (11 g, 1.15 eq) portionwise over a period of 35 minutes. The addition generated a large amount of hydrogen gas. Good stirring was used to prevent frothing.

The resulting suspension was stirred at –78° C. for 4 hours, and then quenched by the dropwise addition of acetic acid (70 ml) over a period of 10 minutes. The solution was warmed to 0° C. and diluted with ethyl acetate (EtOAc) (1.25 L), washed with half-saturated NaCl (500 mlx2) and saturated NaHCO<sub>3</sub> (500 mlx4). The combined aqueous washings were back-extracted with EtOAc (500 mlx2). All of the EtOAc extracts were combined and washed with half-saturated aqueous NaCl (500 mlx1), brine (500 mlx2), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give 69.4 g of the crude title product as a mixture of the diol (R,S)-6-chloro-3,5-dihydroxyhexanoic acid, 1,1-dimethylethyl ester and the corresponding boron complex. At this point, the boron complex was the major component in the crude residue, and about 2.6% of the starting material remained by H-NMR. (TLC: silica gel; EtOAc: Hexane; 1:1; R<sub>f</sub>=0.71, for the boron complex; R<sub>f</sub>=0.44, for the diol; R<sub>f</sub>=0.56, for the starting material.)

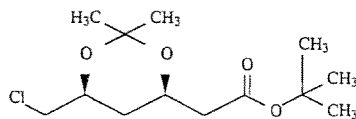
The above crude product (69.4 g) was dissolved in THF (350 ml) and water (140 ml, pH 9, deionized). The pH of the deionized water was adjusted to 9 by the addition of 1N NaOH. To this solution was added dropwise 30% aqueous H<sub>2</sub>O<sub>2</sub> (17.5 ml) over a period of 20 minutes with an ice-water cooling. The addition of H<sub>2</sub>O<sub>2</sub> was exothermic and ice-water cooling was employed to control the temperature between 24° C. and 30° C. The pH of the resulting solution was approximately 6. The reaction was stirred for an additional 30 minutes at room temperature. Then, the solution was titrated with 1N NaOH from pH 6 to pH 7 (about 0.6 ml) and stirred for an additional 30 minutes. (Maintaining a pH of 7 during the stirring period is preferred.)

The reaction solution was poured into a mixture of EtOAc (280 ml) and brine (100 ml). The aqueous layer was separated. The organic layer was washed with saturated NaHCO<sub>3</sub> (120 mlx3) and 20% aqueous NaHSO<sub>3</sub> (100 mlx1). The combined aqueous layer was back-extracted with EtOAc (150 mlx2). All of the EtOAc extracts were combined and washed with saturated NaHCO<sub>3</sub> (150 mlx1), half-saturated aqueous NaCl (120 mlx1), brine (150 mlx2), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give 67 g of the crude diol. This residue was dissolved in hexane (195 ml) and EtOAc (15 ml), and set aside at room temperature for 2 hours and then in the cold room (4° C.) for 16 hours. The crystals were filtered and washed with 1% EtOAc in hexane (50 ml) and dried in vacuo (house low vac) to give 36 g of the pure diol (title product) (calc. 61% from chlorohydrin) as colorless crystals, mp 50°–52° C. (The crude diol prior to

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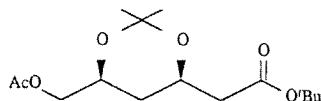
crystallization contained approximately 3% of the hydroxyketone starting material. After crystallization from EtOAc and hexane, the starting material was not detected and the title product was pure by H-NMR.)

(d) (4R-cis)-6-(Chloromethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester



A solution of the diol (R,S)-6-chloro-3,5-dihydroxyhexanoic acid, 1,1-dimethylethyl ester prepared in step (c) above (35.7 g) and camphorsulfonic acid (0.697 g, 0.02 eq) in 2,2-dimethoxypropane (92 ml, 5.0 eq) was stirred at room temperature for 30 minutes in a well-functioning hood. At this point, only a trace amount of diol was present by TLC. (The TLC conditions employed were those described above). The reaction solution was poured into a mixture of EtOAc (100 ml) and saturated NaHCO<sub>3</sub> (150 ml) in a separatory funnel. The aqueous layer was separated and extracted with EtOAc (50 ml). The combined EtOAc layer was washed with half-saturated aqueous NaCl (60 ml x 1), brine (60 ml x 2), dried over MgSO<sub>4</sub>, filtered, and concentrated to give 40.46 g (97%) of the chloroacetone title product as a colorless liquid.

(e) (4R-cis)-6-[(Acetyloxy)methyl]-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester



(i) Preparation of tetra-n-butylammonium acetate

Glacial acetic acid (approximately 23.5 ml) was added dropwise to a stirred 40% aqueous solution of tetrabutylammonium hydroxide (252 ml) in a 1 L three-necked, round bottomed flask fitted with an argon inlet and a pH electrode. During the addition of acetic acid the temperature of the reaction was kept below 35° C. When the pH of the solution reached 8.5 the addition of acetic acid was stopped and the solution was concentrated on a rotary evaporator ≤35° C. under high vacuum (about 0.1 mmHg). The resulting semi-solid was azeotropically dried with toluene (4 x 500 ml) on a rotary evaporator ≤35° C. and then under high vacuum (about 0.1 mmHg) for 24 to 48 hours to afford the white solid (113 grams) tetrabutylammonium acetate. The pH of a solution of 1 gram of the above salt in 2.4 ml of water was 7.66 and 1% aqueous solution was approximately 7.15. The pH of a 1% aqueous solution of tetrabutylammonium acetate is preferably greater than 7.00. (The following conversion to the title compound proceeds at a rapid rate and with a good chemical yield.)

(ii) The displacement reaction

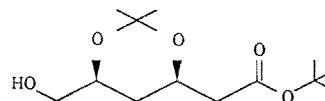
Solid tetrabutylammonium acetate obtained as above (111 g, 0.368 mole) was added in one portion to a mechanically stirred solution of the chloride (4R-cis)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester prepared in step (d) above (35 g, 0.125 mole) in HPLC grade 1-methyl-2-pyrrolidinone (504 ml) under argon. The resulting solution was stirred at 85° C. (internal temperature). After 30 to 60 minutes the reaction mixture became homogeneous and brown in color. The progress of the reaction was followed by TLC and GC analysis. (TLC: R<sub>f</sub>=0.63 for the chloride starting material; R<sub>f</sub>=0.54 for the

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title compound (silica gel, Ethyl acetate:Hexane, 1:1, visualization by Ce(SO<sub>4</sub>)<sub>2</sub> spray). GC: R<sub>f</sub>=7.20 minutes (starting material) and 8.66 minutes (title compound).) After 11 hours the reaction was completed.

The reaction mixture was cooled to room temperature and poured into pH 7.00 phosphate buffer (4 L) and extracted with heptane (3 x 1 L). (It was found from another experiment that the reaction may also be quenched with water instead of pH 7.00 buffer without affecting the yield or the quality of the product.) The organic layers were combined and washed with water (1 L), brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to 1 L and treated with neutral NORIT® (40 grams). The heterogeneous solution was boiled on a water bath for about 2 minutes and filtered hot through a Celite bed on a Buchner funnel. The residue was washed with hot heptane (3 x 250 ml). The filtrates were combined and concentrated on a rotary evaporator under reduced pressure to afford the title compound as a light yellow solid (32.4 grams, 86%). This material was used in the next step without any further purification.

(f) (4R-cis)-6-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester



To a solution of (4R-cis)-6-[(acetyloxy)methyl]-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester (32.2 g, 106 mmole), obtained from the above reaction, in methanol (355 ml), was added powdered anhydrous potassium carbonate (7.34 g, 53.3 mmole) in one portion. The resulting heterogeneous solution was stirred vigorously for 30 minutes to complete the hydrolysis. The solution was filtered through a Buchner funnel and concentrated on a rotary evaporator at room temperature under reduced pressure. Concentration of the reaction mixture at room temperature was employed as concentration at a higher temperature led to the formation of a more polar impurity.

The residue was dissolved in water (250 ml) and extracted with ether (3 x 200 ml). The combined organic layers were washed with water (150 ml), brine (150 ml), dried over MgSO<sub>4</sub>, filtered and concentrated on a rotary evaporator to furnish the title compound as a dark brown oil (28.43 g). This crude product was distilled using a short path distillation apparatus under vacuum. The following fractions were collected.

|                    |                           |
|--------------------|---------------------------|
| Fraction 1: 0.97 g | 95-106° C./0.5 mmHg       |
| Fraction 2: 24.0 g | 106-116° C./0.4-0.15 mmHg |
|                    | 95% GC HI                 |

Fraction 2 contained the title compound along with small amounts of minor impurities as indicated by TLC and <sup>1</sup>H-NMR. This material was therefore redistilled and three fractions were collected.

Fraction 1: 0.5 g 85°-89° C./0.12-0.06 mmHg; 47.3% GC HI

Fraction 2: 1.1 g 89° C./0.08 mmHg; 79.0% GC HI

Fraction 3: 21.1 g 89°-92° C./0.08 mmHg; 98.9% GC HI

Fraction 3 contained the pure title compound (21.1 g, 65% overall yield from the starting material.)

(To avoid the second distillation above, the initial distillation may be carried out through a small Vigreux column.)

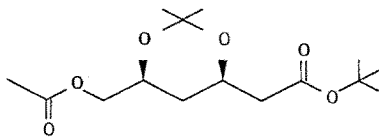


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## EXAMPLE 2

Preparation of  
(4R-cis)-6-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester

(a) (4R-cis)-6-[(Acetyloxy)methyl]-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester

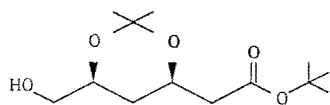


Solid tetra-n-butylammonium acetate prepared in step (i) of Example 1 above (106.2 g, 0.352 mole) was added in one portion to a mechanically stirred solution of the chloride (4R-cis)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester prepared in step (d) of Example 1 above (32.7 g, 0.117 mole) in HPLC grade 1-methyl-2-pyrrolidinone (471 ml) under argon. The resulting solution was stirred at 85° C. (internal temperature). After 30 to 60 minutes the reaction mixture became homogeneous and brown in color. The progress of the reaction was followed by TLC and GC analysis. (TLC:  $R_f=0.54$  for the title compound;  $R_f=0.63$  for the chloride starting material (silica gel, Ethyl acetate: Hexane, 1:1, visualization by  $\text{Ce}(\text{SO}_4)_2$  spray). After 9 hours the reaction was completed.

The reaction mixture was cooled to room temperature and poured into water (4 L) and extracted with heptane (3x1 L). The organic layers were combined and washed with water (1 L), brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to furnish 31.5 grams of a brown solid. It was dissolved in heptane (500 ml) and treated with neutral NORIT® (40 grams). The heterogeneous solution was boiled on a water bath for a few minutes and filtered hot through a celite bed on a Buchner funnel. The residue was washed with hot heptane (3x250 ml).

The filtrates were combined and concentrated on a rotary evaporator under reduced pressure to afford the title compound as a light yellow solid (31.1 grams). This solid was dissolved in hot heptane (60 ml) and allowed to cool slowly to room temperature. During this time off-white crystals began to form. The mixture was kept in the freezer (-20° C.) for 1 hour and the crystals were then filtered, washed with cold heptane (75 ml) and dried in vacuo (approximately 1 mmHg) at room temperature for 3 hours to furnish 24.22 grams (68%) of the title compound as off-white crystals. m.p. 64°-64.5° C.; TLC:  $R_f=0.54$  (silica gel, Ethyl acetate: Hexane, 1:1, visualization by  $\text{Ce}(\text{SO}_4)_2$  spray); GC:  $R_t=7.20$  minutes (chloride starting material) and 8.66 minutes (title compound). 6% of the title compound was also collected as a second crop. The mother liquor (2.60 g) still contained about 20% of the title product as determined by TLC.

(b) (4R-cis)-6-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester



To a solution of (4R-cis)-6-[(acetyloxy)methyl]-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester obtained in step (a) above (22.65 g, 75 mmole) in methanol

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(250 ml) was added powdered anhydrous potassium carbonate (5.17 g, 37.5 mmole) in one portion. The resulting heterogeneous solution was stirred vigorously for 30 minutes to complete the hydrolysis. The progress of the reaction was followed by TLC and GC analysis. (TLC:  $R_f=0.54$  for acetyloxy starting material;  $R_f=0.26$  for the title compound (silica gel, Ethyl acetate:Hexane, 1:1, visualized by  $\text{Ce}(\text{SO}_4)_2$  spray).

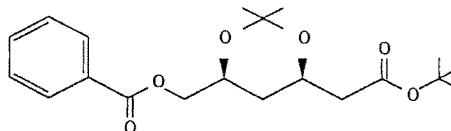
The solution was filtered through a Buchner funnel and concentrated on a rotary evaporator at room temperature under reduced pressure. Room temperature was employed as concentration of the reaction mixture at a higher temperature led to the formation of a more polar impurity. The residue was dissolved in water (250 ml) and extracted with ether (3x200 ml).

The combined organic layers were washed with water (150 ml), brine (150 ml), dried over  $\text{MgSO}_4$ , filtered and concentrated on a rotary evaporator to furnish the title compound as a light yellow oil (19.2 g) in 98% yield. (TLC:  $R_f=0.26$  for the title compound; silica gel, Ethyl acetate:Hexane, 1:1, visualized by  $\text{Ce}(\text{SO}_4)_2$  spray. GC:  $R_t=8.66$  min. (acetyloxy starting material) and 7.32 min. (title compound).)

## EXAMPLE 3

Preparation of  
(4R-cis)-6-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester

(a) (4R-cis)-6-[(Benzoyloxy)methyl]-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester



(i) Preparation of tetra-n-butylammonium benzoate

Benzoic acid (approximately 38 grams) was added portionwise to a stirred 40% aqueous solution of tetrabutylammonium hydroxide (200 ml) in a 1 L three-necked, round-bottomed flask fitted with an argon inlet and a pH electrode. During the addition of benzoic acid the temperature of the reaction was kept below 35° C. When the pH of the solution reached 8.5 the addition of benzoic acid was stopped and the solution was concentrated on a rotary evaporator at  $\leq 35^\circ\text{C}$ . under high vacuum (about 0.1 mmHg). The resulting semi-solid was azeotropically dried with toluene (4x500 ml) on a rotary evaporator at  $\leq 35^\circ\text{C}$ . and then under high vacuum (about 0.1 mmHg) for 24 to 48 hours to afford as a white solid (114 grams) tetrabutylammonium benzoate. KF analysis indicated the presence of 1.20% water in this reagent. The pH of a solution of 2 grams of the above salt in 4 ml of water was 8.29 and a 1% aqueous solution was approximately 7.05. The pH of a 1% aqueous solution of tetrabutylammonium benzoate is preferably greater than 7.00. (The conversion to the title compound described following proceeds rapidly and with a good chemical yield.)

(ii) The displacement reaction

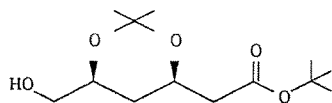
Solid tetrabutylammonium benzoate obtained as above (126.47 g, 0.348 mole) was added in one portion to a mechanically stirred solution of the chloride (4R-cis)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester prepared as in step (d) of Example 1 above (32.3 g, 0.116 mole) in HPLC grade 1-methyl-2-

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pyrrolidinone (465 ml) under argon. The resulting solution was stirred at 100° C. (internal temperature). After 30 to 60 minutes the reaction mixture became homogeneous and brown in color. The progress of the reaction was followed by TLC and GC analysis (TLC:  $R_f=0.47$  for the chloride starting material;  $R_f=0.35$  for the title compound (silica gel, Ether:Hexane, 4:6, visualization by  $\text{Ce}(\text{SO}_4)_2$  spray). After 6.5 hours the reaction was completed.

The reaction mixture was cooled to room temperature and poured into water (4 L) and extracted with heptane (3x1 L). The organic layers were combined and washed with water (1 L), brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to furnish 42.2 grams of a yellow solid. This solid was dissolved in hot heptane (100 ml) and allowed to cool slowly to room temperature. During this time off-white crystals began to form. After standing at room temperature for two hours and at -20° C. (freezer) for one hour the crystals were filtered, washed with cold heptane (75 ml) and dried in vacuo (about 1 mmHg) at room temperature for 3 hours to furnish 33.00 grams of the title compound in 78% yield. An additional 3% of the title product was also collected as a second crop. The mother liquor (4.68 grams) still contained the title product (approximately 75%) as determined by TLC. (TLC:  $R_f=0.35$  Silica gel, Ether:Hexane, 4:6, visualization by  $\text{Ce}(\text{SO}_4)_2$  spray; GC:  $R_f=5.57$  minutes (chloride starting material) and 11.52 minutes (title compound).)

(b) (4R-cis)-6-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester



To a solution of (4R-cis)-6-[(benzoyloxy)methyl]-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester prepared in step (a) above (30.00 g, 82.4 mmole) in methanol (275 ml) was added granular anhydrous potassium carbonate (5.68 g, 41.2 mmole) in one portion. The resulting heterogeneous solution was stirred vigorously for 2 hours to complete the hydrolysis. The progress of the reaction was followed by TLC analysis. (TLC:  $R_f=0.31$  for the benzoyloxy starting material,  $R_f=0.17$  for the title compound (silica gel, Ether:Hexane, 1:1, visualized by  $\text{Ce}(\text{SO}_4)_2$  spray).

The solution was filtered through a Buchner funnel and concentrated on a rotary evaporator at room temperature under reduced pressure. Room temperature was employed as concentration of the reaction mixture at a higher temperature led to the formation of a more polar impurity (uncharacterized). The residue was dissolved in water (500 ml) and extracted with ether (4x250 ml). The combined organic layers were washed with water (3x150 ml), brine (150 ml), dried over  $\text{MgSO}_4$ , filtered and concentrated on a rotary evaporator to furnish the title compound along with methyl benzoate as a colorless oil (32.6 g). This crude product was distilled using a short path distillation apparatus under high vacuum to remove the methyl benzoate. The following fractions were collected.

|            |        |                  |
|------------|--------|------------------|
| Fraction 1 | 5.16 g | 42° C./0.25 mmHg |
| Fraction 2 | 2.71 g | 50° C./0.25 mmHg |
| Fraction 3 | 1.80 g | 52° C./0.25 mmHg |

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-continued

|            |         |                               |
|------------|---------|-------------------------------|
| Fraction 4 | 0.26 g  | 65° C./0.25 mmHg              |
| Fraction 5 | 0.98 g  | 108° C./0.25 mmHg             |
| Fraction 6 | 0.56 g  | (2.6%) 108° C./0.25 mmHg      |
| Fraction 7 | 18.09 g | (84.4%) 108-111° C./0.25 mmHg |

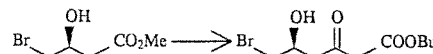
Fraction 1 to Fraction 4 contained mainly methyl benzoate. Fraction 5 was a mixture of methyl benzoate (minor) and the title compound (major). Fraction 6 and Fraction 7 contained only the title compound ( $^1\text{H-NMR}$ ).

Fraction 7: GC: HI 99.00%, TLC:  $R_f=0.17$  for the title compound, Silica gel, Ether:Hexane, 1:1, visualized by  $\text{Ce}(\text{SO}_4)_2$  spray; GC:  $R_f=7.32$  minutes (title compound).

## EXAMPLE 4

Preparation of (4R-cis)-6-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester

(a) (S)-6-Bromo-5-hydroxy-3-oxohexanoic acid, 1,1-dimethylether ester

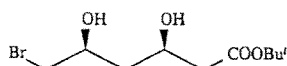


A flame dried 3 L three-necked round bottom flask was charged with tetrahydrofuran (THF) (distilled, 275 ml) and lithium hexamethyldisilazide (LiHMDS) (980 ml, 3.5 eq, 1M solution in THF) at -78° C. The addition of THF was to prevent the LiHMDS from precipitation. To this light brown solution was slowly added tert-butyl acetate ( $\text{CH}_3\text{CO}_2\text{Bu}^t$ ) (151 ml, 4.0 eq) over a period of 10 minutes at -78° C. At the end of the addition, the solution was stirred for another 40 minutes at -78° C. To this light brown homogeneous solution was added a solution of the bromohydrin (S)-4-bromo-3-hydroxybutanoic acid methyl ester (55 g, 0.028 mole, CHIRON, used as purchased) in THF (40 ml) over a period of 20 minutes. The addition was slightly exothermic. The internal temperature climbed from -78° C. to -74° C. during the addition.

The resultant solution was stirred at -78° C. for an additional 1 hour, and then -50° C. for 1 hour. At this point TLC indicated complete reaction. (TLC: silica gel; Ethyl acetate:Hexane, 1:1;  $R_f=0.56$ , UV visualization for the title product;  $R_f=0.55$ , PMA visualization for the bromohydrin starting material.) The reaction solution was slowly transferred via a cannula to a stirred solution of glacial acetic acid (220 ml) in THF (400 ml) at 0° C. The resulting yellow solution was poured into a separatory funnel containing  $\text{H}_2\text{O}$  (800 ml). The aqueous layer was separated and extracted with ethyl acetate (180 mlx2). The combined organic layer was washed with 1N HCl (300 mlx2), and half-saturated NaCl (300 mlx1). The combined HCl and NaCl washings were back extracted with ethyl acetate (300 mlx2). All the ethyl acetate extracts were combined and washed with saturated  $\text{NaHCO}_3$  (400 mlx2), half-saturated NaCl (400 mlx1) and brine (300 mlx2), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give approximately 79 g of the hydroxyketone title product as a brown oil (about 100%). (H-NMR indicated that no starting material remained. The title product was about 80% pure by H-NMR and TLC (same conditions as previously).) The product was used for the next step without any further purification.

(b) (R,S) -6-Bromo-3,5-dihydroxyhexanoic acid, 1,1-dimethylethyl ester

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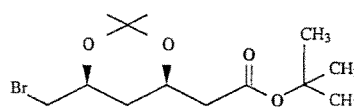
The crude hydroxyketone obtained in step (a) above (79.0 g) was dissolved in THF (1.26 ml) and methanol (MeOH) (HPLC grade, 605 ml) at  $-78^{\circ}\text{C}$ . To this brown solution was added methoxydiethylborane ( $\text{Et}_2\text{BOMe}$ ) (299 ml, 1M solution in THF) over a period of 25 minutes. The addition was slightly exothermic and the solution became cloudy. At the end of the addition, the reaction solution was stirred for an additional 20 minutes. To this cloudy solution was added solid  $\text{NaBH}_4$  (11 g, 1.15 eq.) portionwise over a period of 35 minutes. The addition generated a large amount of hydrogen gas. Good stirring was employed to prevent frothing. The resultant suspension was stirred at  $-78^{\circ}\text{C}$ . for 4 hours. The reaction mixture was slowly added via a cannula to a stirred solution of glacial acetic acid (106 ml) in ethyl acetate (800 ml) at  $0^{\circ}\text{C}$ . The organic solution was separated and washed with half-saturated  $\text{NaCl}$  (400 ml $\times$ 2) and saturated  $\text{NaHCO}_3$  (400 ml $\times$ 4). The combined aqueous washings were back extracted with ethyl acetate (400 ml $\times$ 2). All the ethyl acetate extracts were combined and washed with half-saturated aqueous  $\text{NaCl}$  (400 ml $\times$ 1), brine (400 ml $\times$ 2), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give 85 g of the crude product as a mixture of the diol title product and the corresponding boron complex. At this point, the boron complex was the major component in the crude residue and about 3% of the starting material remained by H-NMR. (TLC: silica gel; Ethyl acetate:Hexane; 1:1,  $R_f$ =0.81, for the boron complex;  $R_f$ =0.44, for the diol title product;  $R_f$ =0.56, for the hydroxyketone starting material.)

The above crude product (85 g) was dissolved in THF (400 ml) and water (350 ml, deionized). To this solution was added 30% aqueous  $\text{H}_2\text{O}_2$  (75 ml). The addition of  $\text{H}_2\text{O}_2$  was exothermic and ice-water cooling was employed to control the temperature between  $24^{\circ}\text{C}$ . and  $30^{\circ}\text{C}$ . The pH of the resulting solution was about 6. Addition of 1N  $\text{NaOH}$  (approximately 20 ml) followed to maintain the pH of this solution equal to 7. The resultant mixture was stirred for an additional 30 minutes at room temperature. The solution was maintained at pH 7 throughout the reaction period.

The reaction solution was poured into a mixture of ethyl acetate (275 ml) and brine (110 ml). The aqueous layer was separated. The organic layer was washed with saturated  $\text{NaHCO}_3$  (400 ml $\times$ 3) and 10% aqueous  $\text{NaHSO}_3$  (200 ml $\times$ 1). The combined aqueous layer was back extracted with ethyl acetate (200 ml $\times$ 2). All the ethyl acetate extracts were combined and washed with saturated  $\text{NaHCO}_3$  (300 ml $\times$ 1), half-saturated aqueous  $\text{NaCl}$  (200 ml $\times$ 1) and brine (300 ml $\times$ 3), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give 70 g of the crude diol title product. This residue was dissolved in hexane (180 ml) and ethyl acetate (8 ml), seeded and set aside at room temperature for 2 hours and then in the cold room ( $4^{\circ}\text{C}$ .) for 16 hours. The crystals were filtered and washed with 1% ethyl acetate in hexane (30 ml) and dried in vacuo (low house vac) to give 27 g of the pure diol title product (calc. 34% from (S)-4-bromo-3-hydroxybutanoic acid methyl ester) as colorless crystals, mp  $43.5^{\circ}$ – $46^{\circ}\text{C}$ .

(c) (4R-cis)-6-(Bromomethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester

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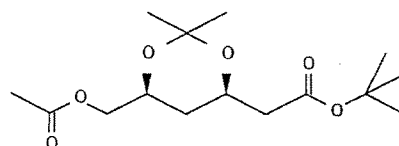


A solution of the diol obtained in step (b) above (25.4 g, 90 mmol) and camphorsulfonic acid (0.209 g, 0.01 eq) in 2,2-dimethoxypropane (55 ml, 5.0 eq) (note: as 2,2-dimethoxypropane may cause eye irritation, operations with this material should be carried out in a well-functioning hood) was stirred at room temperature for 40 minutes. At this point, only a trace amount of the diol starting material was present by TLC. (TLC conditions as previously described). The reaction solution was poured into a mixture of ethyl acetate (300 ml) and saturated  $\text{NaHCO}_3$  (300 ml) in a separatory funnel. The aqueous layer was separated and extracted with ethyl acetate (50 ml). The combined ethyl acetate layer was washed with half-saturated aqueous  $\text{NaCl}$  (60 ml $\times$ 1), brine (60 ml $\times$ 2), dried over  $\text{MgSO}_4$ , filtered, and concentrated to give 27.0 g (97%) of the bromoacetone diol title product as a pale yellow liquid.

|    | Elemental Analysis (%)                   |       |
|----|--|-------|
|    | $\text{C}_{13}\text{H}_{23}\text{BrO}_4$ |       |
|    | Calc.                                    | Found |
| C  | 48.31                                    | 48.80 |
| H  | 7.17                                     | 7.29  |
| Br | 24.72                                    | 24.85 |

$[\alpha]_D^{25} = +7.78$  (c 1.0, MeOH),  $[\alpha]_{365} = +31.52$  (c 1.0, MeOH) TLC:  $R_f$ =0.55; Ethyl acetate:Hexane; 3:7; Silica gel; UV and PMA Visualization; HPLC: HI=89.5, II 0.4 for anti acetone diol, II 0.2 for hydroxyketone and II 9.9 for total unknowns. (HI stands for Homogeneity Index; II stands for Impurity Index).

(d) (4R-cis)-6-[(Acetyloxy)methyl]-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester



Solid tetrabutylammonium acetate (62.4 g, 0.207 mole, commercially available reagent was used) was added in one portion to a stirring solution of the bromoacetone diol obtained in step (c) above (22.3 g, 0.068 mole) in 1-methyl-2-pyrrolidinone (276 ml, commercially available HPLC grade, used as purchased) under an argon atmosphere. The resulting solution was stirred at  $90^{\circ}\text{C}$ . (external temperature) for 1 hour (after a few minutes the reaction mixture became brown in color) to complete the reaction. (The progress of the reaction was followed by TLC,  $R_f$ =0.48 for the title product;  $R_f$ =0.63 for the bromoacetone diol starting material (Silica gel, Ethyl acetate:Hexane, 1:1, visualization by  $\text{Ce}(\text{SO}_4)_2$  spray).) The reaction mixture was cooled to room temperature and poured into water (1.5 L) and extracted with heptane (4 $\times$ 800 ml). The organic layers were combined and washed with water, brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to furnish 18.45 grams of a brown solid. It was dissolved in heptane (250 ml) and treated with neutral NORIT® (25 grams).

The heterogeneous solution was boiled on a water bath for 5 minutes and filtered hot through a celite bed on a Buchner

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funnel. The residue was washed with hot heptane (3×150 ml). The filtrates were combined and concentrated on a rotary evaporator under reduced pressure to afford the title product as a light yellow solid (17.6 grams). This solid was dissolved in hot heptane (40 ml) and allowed to cool slowly to room temperature and during this time off-white crystals began to form. It was kept in the cold room (-5° C.) overnight and the crystals were filtered, washed with cold heptane (50 ml) and dried in vacuo (about 1 mmHg) at room temperature for 3 hours to furnish 14.47 grams (69.5%) of the title product as off-white crystals. An additional 7.5% of the title product was also collected as a second crop. m.p. 64°-65° C.; TLC:  $R_f$ =0.48 (Silica gel, Ethyl acetate:Hexane, 1:1 visualization by  $Ce(SO_4)_2$  spray).

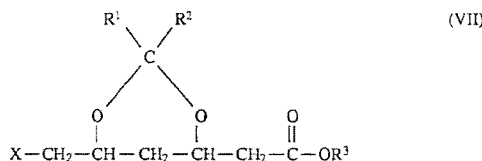
|   | Elemental Analysis (%) |       |
|---|------------------------|-------|
|   | $C_{15}H_{26}O_6$      |       |
|   | Calc.                  | Found |
| C | 59.58                  | 59.64 |
| H | 8.67                   | 8.94  |

(e) (4R-cis)-6-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester

(4R-cis)-6-[(Acetyloxy)methyl]-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester obtained in step (d) above is converted to the title product according to the procedure of Example 1, step (f).

What is claimed is:

1. A method for the preparation of a compound of the formula VII:

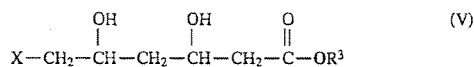


where

X is a halogen atom;

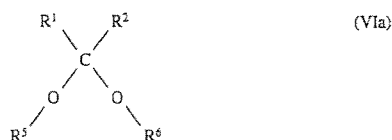
$R^1$  and  $R^2$  are each independently hydrogen, an alkyl group, a cycloalkyl group, an aryl group or, taken together with the carbon atom to which they are attached, form a cycloalkyl group; and

$R^3$  is hydrogen, an alkyl group or an aryl group, or a pharmaceutically acceptable salt thereof, comprising the step of reacting a compound of the formula V:



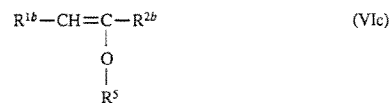
where

X and  $R^3$  are as defined in the formula VII, or a pharmaceutically acceptable salt thereof, with a compound of the formula VIa, VIb or VIc:



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-continued



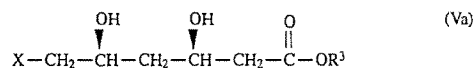
where

$R^1$  and  $R^2$  are as defined in the formula VII;

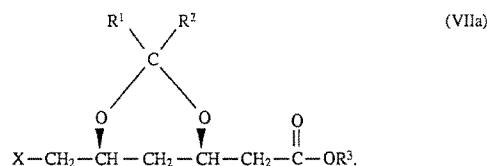
$R^{1b}$  and  $R^{2b}$  are each independently hydrogen, an alkyl group, a cycloalkyl group, an aryl group or, taken together with the carbon atoms to which they are attached, form a 1,2-cycloalkenyl group; and

$R^5$  and  $R^6$  are each independently an alkyl group, in the presence of an acidic condensation agent, wherein alkyl employed herein alone or as part of another group has from 1 to 21 carbons; cycloalkyl employed herein alone or as part of another group has from 3 to 21 carbons; aryl employed herein alone or as part of another group has from 6 to 12 carbons; cycloalkenyl employed herein alone or as part of another group has from 3 to 21 carbons.

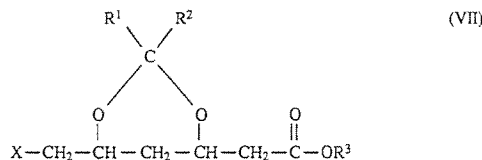
2. The method of claim 1, wherein a compound or pharmaceutically acceptable salt thereof having the stereoisomeric configuration Va is employed:



and wherein a compound or pharmaceutically acceptable salt thereof having the stereoisomeric configuration VIIa is prepared:



3. A compound of the formula VII:



where

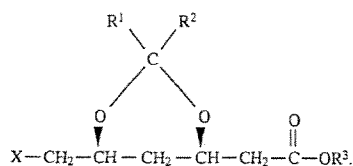
X is a halogen atom;

$R^1$  and  $R^2$  are each independently hydrogen, an alkyl group, a cycloalkyl group, an aryl group or, taken together with the carbon atom to which they are attached, form a cycloalkyl group; and

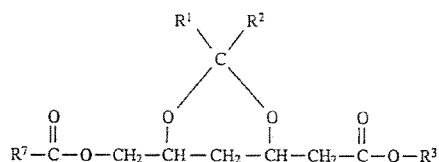
$R^3$  is hydrogen, an alkyl group, or an aryl group, or a pharmaceutically acceptable salt thereof, wherein alkyl employed herein alone or as part of another group has from 1 to 21 carbons; cycloalkyl employed herein alone or as part of another group has from 3 to 21 carbons; aryl employed herein alone or as part of another group has from 6 to 12 carbons.

4. The compound as defined in claim 3, wherein said compound or pharmaceutically acceptable salt thereof has the stereoisomeric configuration VIIa:

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5. A method for the preparation of a compound of the formula VIII:

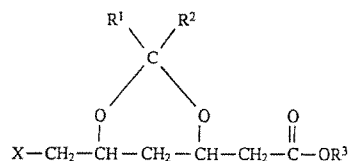


where

$R^1$  and  $R^2$  are each independently hydrogen, an alkyl group, a cycloalkyl group, an aryl group or, taken together with the carbon atom to which they are attached, form a cycloalkyl group;

$R^3$  is hydrogen, an alkyl group or an aryl group; and

$R^7$  is an alkyl group or an aryl group; or a pharmaceutically acceptable salt thereof, comprising the step of displacing the group X of a compound of the formula VII:



where

x is a halogen atom; and

$R^1$ ,  $R^2$  and  $R^3$  are as defined in the formula VIII,

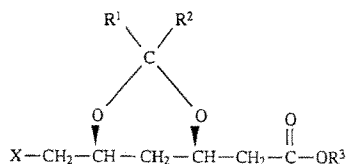
or a pharmaceutically acceptable salt thereof, with an acyloxy group of the formula  $-O-C(=O)-R^7$ , by use of a displacement agent,

wherein alkyl employed herein alone or as part of another group has from 1 to 21 carbons;

cycloalkyl employed herein alone or as part of another group has from 3 to 21 carbons;

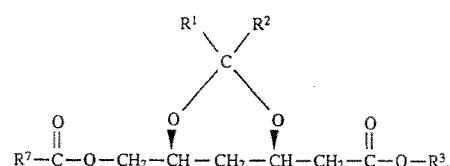
aryl employed herein alone or as part of another group has from 6 to 12 carbons.

6. The method of claim 5, wherein a compound or pharmaceutically acceptable salt thereof having the stereoisomeric configuration VIIa is employed:

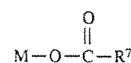


and wherein a compound or pharmaceutically acceptable salt thereof having the stereoisomeric configuration VIIa is prepared:

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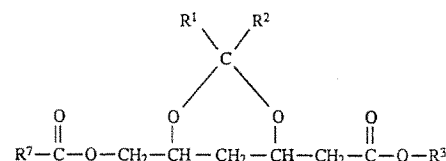
7. The method of claim 5, wherein a compound of the formula IX:



where

M is a metal or an ammonium group; and  $R^7$  is as defined for the formula VIII, is employed as said displacement agent.

8. A compound of the formula VIII:



where

$R^1$  and  $R^2$  are each independently hydrogen, an alkyl group, a cycloalkyl group, an aryl group or, taken together with the carbon atom to which they are attached, form a cycloalkyl group;

$R^3$  is hydrogen, an alkyl group or an aryl group; and

$R^7$  is an alkyl group,

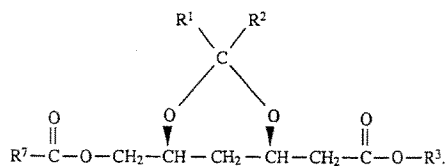
of a pharmaceutically acceptable salt thereof,

wherein alkyl employed herein alone or as part of another group has from 1 to 21 carbons;

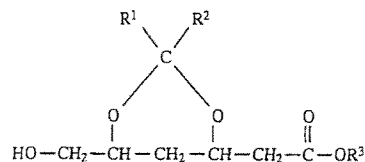
cycloalkyl employed herein alone or as part of another group has from 3 to 21 carbons;

aryl employed herein alone or as part of another group has from 6 to 12 carbons.

9. The compound as defined in claim 8, wherein said compound or pharmaceutically acceptable salt thereof has the stereoisomeric configuration VIIIa:



10. A method for the preparation of a compound of the formula I:



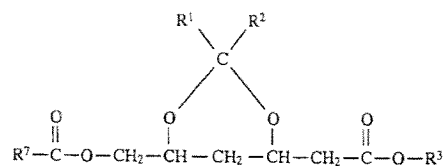
where

$R^1$  and  $R^2$  are each independently hydrogen, an alkyl group, a cycloalkyl group, an aryl group or, taken together with the carbon atom to which they are attached, form a cycloalkyl group; and

$R^3$  is hydrogen, an alkyl group, or an aryl group;

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or a pharmaceutically acceptable salt thereof:



where

$\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$  are as defined in the formula I, and

(i)  $\text{R}^7$  is an alkyl group; or

(ii) said hydrolysis is conducted employing a mild base and/or a mildly basic medium and  $\text{R}^7$  is an alkyl group or an aryl group,

wherein alkyl employed herein alone or as part of another group has from 1 to 21 carbons;

cycloalkyl employed herein alone or as part of another group has from 3 to 21 carbons;

aryl employed herein alone or as part of another group has from 6 to 12 carbons.

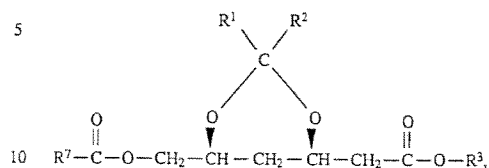
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11. The method of claim 10, wherein a compound or pharmaceutically acceptable salt thereof having the stereoisomeric configuration VIIIa is employed:

(VIII)

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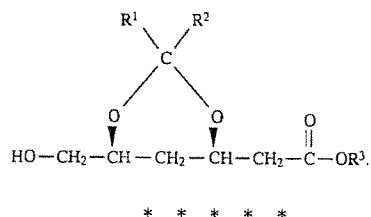
(VIIIa)



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and wherein a compound or pharmaceutically acceptable salt thereof having the stereoisomeric configuration Ia is prepared:

(Ia)



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**Exhibit C**

# Phase-Transfer Catalysis Communications

## Choosing a Phase-Transfer Catalyst for the First Experiment

Marc E. Halpern

PTC Technology, Suite 627, 1040 North Kings Highway, Cherry Hill,  
New Jersey 08034 USA; Phone 1 609 321 1477; Fax 1 609 321 1544;  
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**Summary:** The purpose of the first experiment of a screening program for a new PTC application is to determine if the reaction produces product. Therefore, maximizing reactivity should usually be the focus of the first experiment. Unless data are available to suggest the use of a specific catalyst, it is suggested to choose a catalyst for the first experiment, which is likely to induce reactivity in the widest range of reactions. The catalysts which are most likely to induce reactivity in most PTC categories are Aliquat 336® and tetrabutyl ammonium hydrogen sulfate.

Everyone wants their process improvement or new process development project to show early success. If you are producing organic chemicals, there is a good chance that phase-transfer catalysis, "PTC," will help you achieve high process performance. Which catalyst do you choose, when you first start evaluating a new PTC application? Why do you choose that catalyst? That first choice of catalyst can make a big difference.

Unless a specific literature reference is available recommending a specific catalyst for a specific PTC reaction, chemists may just choose for the first experiment whatever is "on the shelf," usually tetrabutyl ammonium bromide (TBAB) or tetrabutyl ammonium hydrogen sulfate (TBAHSO<sub>4</sub>), sometimes Aliquat 336® (MeN[C<sub>18</sub>H<sub>37</sub>]<sub>3</sub> Cl) or triethyl benzyl ammonium chloride (TEBAC). Choosing a convenient catalyst off the shelf for the first screening experiment is often a reasonable thing to do, if that catalyst is a good "all purpose" catalyst and it allows you to try the idea while it is still fresh.

### Criteria for an All-Purpose PTC "Shelf Catalyst" for Screening

When you start a lab evaluation of a new PTC idea (screening stage), you want to maximize the probability of reaching a firm conclusion, and hopefully, a promising result in the first few experiments. During this early stage screening, the goal is to find out if PTC will work at all for the candidate reaction. The goal is *not* to discover a fully optimized process, product purification scheme, lowest cost catalyst, etc. during the first

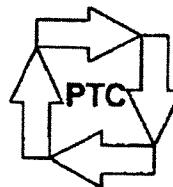
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experiment. The key observation sought, especially during the first experiment, is appearance of product. Therefore, in the first experiment we usually try to stack the deck in favor of maximizing reactivity.

### Background for Discussing "Screening Catalysts"

A review of thousands of PTC publications and patents consistently reveals that chemists usually choose from among a handful of phase-transfer catalysts for screening. These include TBAB, TBAHSO<sub>4</sub>, Aliquat 336<sup>®</sup> and TEBAC. TBAB is by far the most highly reported catalyst. In fact, a surprising number of publications as well as patents, report the use of TBAB and never provide an example of any other catalyst. This is especially surprising for patents, for which the driving force of economic feasibility should dictate attempting to identify the "optimal" catalyst. A screening program using just one catalyst may be acceptable if the goal of the project is just to "make some" product. However, if the goal is to obtain the product in high yield in the lab/plant or to achieve a short cycle time in the plant, more than one catalyst should be screened before publication or patent filing. Since in a surprisingly large number of cases, the first catalyst tried is the only one ever reported (usually TBAB), then it is particularly important to choose the best catalyst for screening.

Sometimes polyethylene glycols, other ammonium salts (e.g., tetrahexyl ammonium bromide), phosphonium salts (e.g., hexadecyl tributyl phosphonium bromide) and crown ethers are screened during the first few experiments. These are good catalysts and are appropriate for comprehensive screening programs. In fact, more catalysts should be added to this list such as methyltributyl ammonium chloride and selected polypodands. However, time management pressures often dictate very limited screening programs and TBAB/HSO<sub>4</sub>, Aliquat 336<sup>®</sup> and TEBAC are overwhelmingly screened. One of the driving forces for writing this article is having observed projects being dropped after only one experiment which provided negligible or 0% conversion. [This is especially frustrating and applicable to projects in which the first experiment used the popular TEBAC catalyst]. Therefore, the purpose of this article is to present an underlying thought process and supporting data for choosing a phase-transfer catalyst which should be kept on the shelf of every organic chemist for use in first experiments. The catalyst chosen for screening new applications should be readily available and have the highest likelihood of inducing reasonably high reactivity in the broadest range of organic reactions.

Please note that this article does not suggest that a single phase-transfer catalyst will meet all of the criteria for commercial development. Each PTC application is unique and will require a proper determination of the optimal catalyst. There are many commercial PTC applications which are best performed with each of the catalysts discussed and others. This article focuses on the first experiment only because in every project, a first experiment is inevitable and a choice of catalyst must be made.

### Catalyst Factors Which Affect Reactivity

When considering common quaternary ammonium salts as phase-transfer catalysts, there are five major catalyst structure factors which affect reactivity in the PTC application: (1) organophilicity, (2) accessibility of the positive charge of the nitrogen, (3) counteranion, (4) stability and (5) interfacial tension (sometimes). The ultimate choice of catalyst for the final commercial PTC process will take into account other factors such as catalyst separation, catalyst cost, catalyst availability, toxicity, and solubility in waste streams. If a single phase-transfer catalyst was commercially available which was better than most other commercially available phase-transfer catalysts, in *all reactivity attributes*, then it would be an excellent candidate for screening in the first experiment. If the catalyst also meets the other process criteria such as cost, separation and likelihood of contaminating an aqueous waste stream, then it would indeed be a very good commercial phase-transfer catalyst. The following discussion will show that Aliquat 336<sup>®</sup> and TBAHSO<sub>4</sub> are probably the best catalysts for screening new PTC applications for reactivity. TEBAC is *sometimes* an excellent catalyst for reactivity, but it is *not* "universal." TEBAC is totally ineffective in several major reaction categories. Aliquat 336<sup>®</sup> and TBAHSO<sub>4</sub> almost always work.

### Reactivity and Mechanism

Several mechanisms are usually at work during PTC reactions, but usually a combination of two processes dominates the rate behavior.<sup>1</sup> These processes are (1) the intrinsic reaction, usually occurring in the organic phase and (2) transfer, usually of anion from an aqueous or solid phase to an organic phase. Reactions in which the reaction rates are limited by the intrinsic reaction are termed "I-reactions." Reactions in which the reaction rates are limited by transfer are termed "T-reactions."

The rate determining step of an I-reaction is the attack of a nucleophile, base, oxidizing agent or other anion

<sup>1</sup> Starks, C.; "Phase-Transfer Catalysis: Mechanism and Syntheses, ACS Symposium Series 659," Halpern, M. ed., American Chemical Society, Washington DC, 1997, Chapter 2

associated with the quat on the substrate. Under certain reaction conditions, the rate expression of I-reactions can simply be:

$$\text{rate} = k_{\text{chem}}[\text{QX}]_{\text{org}}[\text{substrate}]_{\text{org}}$$

where  $k_{\text{chem}}$  is the rate constant of the chemical reaction and  $[\text{QX}]_{\text{org}}$  is the concentration of the ion pair between the quat and the desired reacting anion,  $\text{X}^-$ , in the organic phase in which the reaction takes place. According to this rate expression, the structure of the catalyst can affect the rate of such I-reactions in four major ways:

- (1) being *organophilic* enough to solubilize the reacting anion,  $\text{X}^-$ , in the organic phase, thereby increasing  $[\text{QX}]_{\text{org}}$
- (2) being introduced with a *less polarizable counteranion* which does not strongly associate with the quat, thereby providing less competition to  $\text{X}^-$  for extraction into the organic reaction phase and increasing  $[\text{QX}]_{\text{org}}$
- (3) being *stable* enough under the reaction conditions to continue to be active and extract  $\text{X}^-$  into the organic reaction phase, thereby increasing  $[\text{QX}]_{\text{org}}$
- (4) forming a *loose ion pair* with  $\text{X}^-$  thereby enhancing its reactivity by increasing  $k_{\text{chem}}$

The most common quats used for screening in the literature are TBAB/ $\text{HSO}_4^-$ , Aliquat 336<sup>®</sup> and TEBAC and are compared based on their attributes for I-reactions in Table 1.

- (1) For I-reactions, quats are considered organophilic from about 16 carbons and are effective up to about 32 carbons. Below 16 carbons, quats often induce no reactivity (see for example, the  $\text{S}_{\text{N}}2$  reaction of

Table 1: Catalyst Structure Comparison for I-Reactions

|                 | TBAB/ $\text{HSO}_4^-$     | Aliquat 336 <sup>®</sup> | TEBAC         |
|-----------------|----------------------------|--------------------------|---------------|
| organophilicity | 16 carbons                 | ~25 carbons              | 13 carbons    |
| counteranion    | $\text{Br}/\text{HSO}_4^-$ | $\text{Cl}^-$            | $\text{Cl}^-$ |
| stability       | med                        | med-hi                   | low           |
| loose ion pair  | $q = 1$                    | $q = 1.4$                | $q = 1.6$     |

thiophenol with octyl bromide<sup>2</sup> or the isomerization of allylbenzene<sup>3</sup>). Above 32 carbons, the quats become

<sup>2</sup> Herriott, A.; Picker, D.; J. Amer. Chem. Soc., 1975, 97, 2345

less effective due to difficulty in extracting anions from the aqueous or solid phase resulting from their large footprint at the interface (low concentration) and the shielding of the positive charge.<sup>1</sup> Aliquat 336<sup>®</sup> has approximately 25 carbons and most salts of this catalyst are nearly totally soluble in common organic solvents. Tetrabutyl ammonium (TBA) salts generally distribute between the aqueous and organic phases. If, for example, a TBA salt is 2/3 distributed into the organic phase and the corresponding methyltricaprylyl ammonium salt is totally soluble in the organic phase, then the  $[\text{QX}]_{\text{org}}$  term will be affected accordingly. TEBA salts are often not very soluble in organic solvents. Even TEBA salts of anions which are usually easily extracted into chlorinated hydrocarbons (e.g.,  $\text{MnO}_4^-$ )<sup>4</sup> are not nearly as soluble as the TBA salts. When using even less polar solvents, the differences in  $[\text{QX}]_{\text{org}}$  can be quite dramatic. For example, in toluene (more common in modern commercial applications which prefer to avoid chlorinated hydrocarbons), the solubility of  $\text{MeNOct}^+$ ,  $\text{MnO}_4^-$  is 0.8M while TBA  $\text{MnO}_4^-$  is only 0.00034M.<sup>5</sup>

- (2) Usually, introducing the quat with a less polarizable counteranion is desirable. Chloride is usually preferred over bromide, since the relative extractability of monoanions ( $\text{X}^-$ ) is 3-50 times higher in the presence of chloride relative to bromide.<sup>6</sup> Aliquat 336<sup>®</sup> and TEBAC contain chloride compared to the bromide of TBAB. TBA chloride may be a good catalyst, but is not readily available commercially (it is made from the bromide). TBA $\text{HSO}_4^-$  is usually advantageous over the chloride and bromide and indeed this catalyst is often a good screening catalyst (it is much more expensive than the other three common catalysts but is readily available).

The extractability of dianions is sometimes enhanced by diquat ion pairs.<sup>7</sup> The ion pairs between dianions and common quats show interesting behavior (Table 2).

In some cases, the bromide and even the iodide can actually induce higher reactivity than the chloride. This occurs when the organic substrate can be activated by converting it to a bromide which may be more reactive.

<sup>1</sup> Halpern, M.; Sasson, Y.; Rabinovitz, M.; J. Org. Chem., 1983, 48, 1022

<sup>4</sup> Herriott, A.; Picker, D.; Tetrahedron Lett., 1974, 1511

<sup>5</sup> cited in Starks, C.; Liotta, C.; Halpern, M.; "Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives," 1994, Chapman and Hall, New York p. 502

<sup>6</sup> see ref 5, pp. 27, 31 and 35 based on references cited therein

<sup>7</sup> Lissel, M.; Feldman, D.; Nir, M.; Rabinovitz, M.; Tetrahedron Lett., 1989, 1683

Table 2: Extractability of Selected Dianions

| quat salt                             | $\text{Cr}_2\text{O}_7^{2-}$ | $\text{Fe}(\text{CN})_6^{3-}$ | phthalate    |
|---------------------------------------|------------------------------|-------------------------------|--------------|
| $\text{Oct}_3\text{NMe}^+\text{Cl}^-$ | 0.56                         | 0.32                          | 0.17         |
| TBA $\text{HSO}_4^-$                  | 0.59                         | <0.03                         | 0.08         |
| TBAB                                  | 0.47                         | 0.04                          | 0.05         |
| TEBAC                                 | 0.01                         | 0.02                          | not reported |

For example, an alkyl chloride alkylating agent can be converted to an alkyl bromide alkylating agent by the attack of the bromide introduced with the quat. *This happens more often than is probably realized by academic and commercial PTC development teams.*

Nevertheless, the chloride counteranion usually induces higher reactivity than bromide. This is especially true when there are no leaving groups such as bromide or tosylate. Thus,  $\text{ClO}^-$  oxidations,<sup>8</sup> isomerizations<sup>3</sup> and deuterations are usually much more active with the counteranions:  $\text{HSO}_4^- > \text{Cl}^- > \text{Br}^-$ .

In addition,  $\text{S}_\text{N}2$  reactions, such as alkylation, cyanation, azide preparation, etc. will liberate a bromide or chloride leaving group. After significant reaction occurs (for example 50 mole%), the catalyst counteranion (present at only 1-5 mole%) will be "outnumbered" by the leaving group anion and the catalyst counteranion will no longer significantly affect the reaction rate. Thus, in such cases, the reaction rate is mostly affected by the catalyst counteranion at the outset of the reaction. So as not to minimize the importance of the beginning of the reaction, it should be remembered that the economics of a chemical process depend significantly on the process cycle time (reactor hours) and any improvement (i.e., reduction) in cycle time translates into profit.

(3) Stability studies showed that Aliquat 336<sup>®</sup> is approximately 70% more stable than TBA chloride, approximately 2.5 times more stable than benzyl trihexyl ammonium chloride and 4-5 times more stable than TEBAC in the presence of 50% NaOH at 25°C.<sup>9</sup>

(4) The looseness of the ion pair is related to the accessibility of the positive charge on the nitrogen atom of the quat. An empirical parameter, "q," which may represent accessibility was suggested<sup>10</sup> and is calculated by adding the reciprocals of the number of carbons on

each chain of the quat. If this parameter is representative of accessibility of the positive charge then a lower q value should result in a looser ion pair and should induce higher reactivity. TBA should then induce higher reactivity than Aliquat 336<sup>®</sup> which in turn should induce higher reactivity than TEBA.

When taking into account the catalyst structure effects discussed above which influence the rate of I-reactions, it may be concluded that Aliquat 336<sup>®</sup> is more likely to give higher reactivity than TBAB, though both would work. TBAHSO<sub>4</sub> will usually work better than TBAB. TEBAC is rarely an acceptable catalyst for I-reactions. Since we usually do not know for sure before the first experiment if the candidate reaction will be an I-reaction or a T-reaction, then we should eliminate TEBAC from the "short list" of catalysts to be screened for the first experiment of a totally new PTC project.

Following are examples PTC reactions believed to be I-reactions. Comparisons of catalysts are highlighted when available.

#### Example Reactions - Esterification

Esterification is one of the most highly patented reactions using PTC. The classical PTC patent of all time by Starks reports the quantitative esterification of acetate in example 6.<sup>11</sup> Aliquat 336<sup>®</sup> was chosen as the catalyst for this reaction as well as for 20 other examples of nucleophilic substitutions and oxidations.

Esterifications are usually performed without the addition of solvent since the starting materials and/or products are usually liquid and their structures (such as alkyl halides) are appropriate to serve as effective "solvents" for PTC.

When reporting on the comparison of Aliquat 336<sup>®</sup> with TBAB for acetate esterifications (see Table 3), Bram et al<sup>12</sup> wrote: "Aliquat 336<sup>®</sup> is far superior to  $\text{NBu}_4\text{Br}$  for acetate alkylation performed with  $\text{nC}_4\text{H}_9\text{Br}$ ,  $\text{nC}_8\text{H}_{17}\text{Br}$  and  $\text{nC}_{16}\text{H}_{33}\text{Br}$ ; alkyl acetates are thus obtained with yields >92% at room temperature." The difference in reactivity disappears for highly reactive alkylating agents such as benzyl bromide.

Aliquat 336<sup>®</sup> and TBAHSO<sub>4</sub> were screened for transesterification of methyl esters (see Table 4).<sup>13</sup> The

<sup>8</sup> Lee, G.; Freedman, H.; (Dow Chemical), 1978, US Patent 4,079,075

<sup>9</sup> Landini, D.; Maia, A.; Rampoldi, A.; J. Org. Chem., 1986, 51, 3187

<sup>10</sup> ref 5, p. 281

<sup>11</sup> Napier, D.; Starks, C.; (Continental Oil) US Patent 3,992,432 (1976)

<sup>12</sup> Bram, G.; Loupy, A.; Sansoulet, J.; Isr. J. Chem., 1985, 26, 291

<sup>13</sup> Barry, J.; Bram, G.; Petit, A.; Tetrahedron Lett., 1988, 4567

reason for the reversal of the effect of catalyst on the yields of these two esterifications is not clear.

In the polyesterification reaction between bisphenol-A and the diacid chloride  $\text{ClCOPhC(CH}_3)_2\text{PhCOCl}$ , the order of reactivity and inherent viscosity increase was Aliquat 336<sup>®</sup> > TBAB >> TEBAC (see Table 5).<sup>14</sup>

Table 3: Effect of Catalyst on Esterification

|   |              |          |                 |
|---|--------------|----------|-----------------|
| $\text{CH}_3\text{COO}^-\text{K}^+ + \text{C}_8\text{H}_{17}\text{Br} \xrightarrow[2\text{h, } 60^\circ\text{C}]{\text{Q}^+\text{X}^- \text{ 3 mol\%}} \text{CH}_3\text{COOC}_8\text{H}_{17}$ |              |          |                 |
|   | 2h/60°C      | 20h/r.t. | 20h/r.t./10mol% |
| Aliquat 336 <sup>®</sup>  | 98%          | 68%      | 98%             |
| TBAB  | 73%          | 2%       | not reported    |
| TEBAC   | not reported |          |                 |

Reaction conditions: 11 mmol  $\text{CH}_3\text{COOK}$ , 10 mmol OctBr, 3mol% QX unless stated otherwise, time and temp as shown; no water, no added solvent

Table 4: Effect of Catalyst on Transesterification

|  |           |                          |                     |
|--|-----------|--------------------------|---------------------|
| $\text{C}_6\text{H}_5\text{C(=O)OCH}_3 + \text{ROH} \xrightarrow[20\text{mol\%}]{\text{QX 2mol\%}, \text{K}_2\text{CO}_3 \text{ 1equiv}} \text{C}_6\text{H}_5\text{C(=O)OR}$ |           |                          |                     |
| ROH  | time/temp | Aliquat 336 <sup>®</sup> | TBAHSO <sub>4</sub> |
| 2-ethylhexan-1-ol  | 55°C/3h   | 99%                      | 10%                 |
| 2-octanol  | 70°C/10h  | 13%                      | 72%                 |

### Example Reactions - O-Alkylation (Etherification)

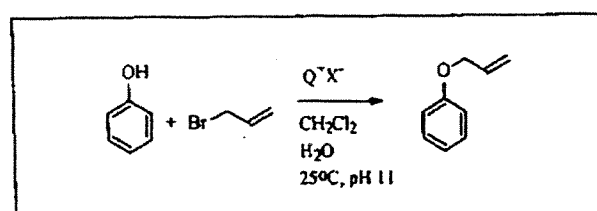
The first PTC O-alkylations published were landmark publications for synthesis (typically 90-100% yield) and reported one catalyst each (TBAB,<sup>15</sup> benzyl tributyl ammonium chloride<sup>16</sup> and TBA iodide<sup>17</sup>). More recently, the extraction of phenol from a simulated waste stream (5000 ppm) and reaction with allyl bromide showed that the more organophilic catalysts

Table 5: Effect of Catalyst on Polyesterification

|                          |       |               |
|--------------------------|-------|---------------|
|                          | Yield | $\eta$ (dl/g) |
| Aliquat 336 <sup>®</sup> | 90%   | 0.50          |
| TBAB                     | 81%   | 0.17          |
| TEBAC                    | 48%   | 0.11          |

Reaction conditions: 2.5mmol bisphenol-A, 5mol% catalyst, 25 mL 0.3M NaOH, 20 mL water, 20 mL  $\text{CH}_2\text{Cl}_2$ , 2.625 mmol diacid, 5 mL  $\text{CH}_2\text{Cl}_2$ , 20°C, 60 min

gave higher rates of phenol consumption.<sup>18</sup> In this case it would appear that organophilicity is more important than counteranion. It is interesting that tetrabutyl phosphonium bromide gave a rate of 5.25 M/min, which is nearly double that of TBAB. Phosphonium salts are more lipophilic than ammonium salts.

Table 6: Effect of Catalyst on O-Alkylation<sup>18</sup>

|                          |              |
|--------------------------|--------------|
| catalyst                 | rate (M/min) |
| Aliquat 336 <sup>®</sup> | 6.37         |
| TBAHSO <sub>4</sub>      | 3.45         |
| TBA Br                   | 2.29         |
| TEBA Cl                  | 0.163        |

Reaction conditions: 50mL aqueous phase containing 5000 ppm phenol at pH 11; 83 mmol allyl bromide, 0.62 mmol QX, 50 mL  $\text{CH}_2\text{Cl}_2$ ; 25°C

Bram et al compared several PTC and non-PTC etherification systems (for example, the reaction of n-octanol with methyl iodide) and reported "It is apparent that the use of KOH/Aliquat without solvent is the best method; not only is it very easy to perform and inexpensive, but the yield is quantitative within 2 h at room temperature."<sup>12</sup>

### Example Reactions - S-Alkylation

The first publication to report a comprehensive screening of catalysts for any PTC reaction was for the alkylation of thiophenol (see Table 7).<sup>2</sup> The paper is one of the classic PTC publications. Aliquat 336<sup>®</sup> outperformed 19 other catalysts except for two

<sup>14</sup> Tagle, L.; Diaz, F.; Campbell, W.; Eur. Polym. J., 1993, 29, 1069

<sup>15</sup> Freedman, H.; DuBois, R.; Tetrahedron Lett., 1975, 3251

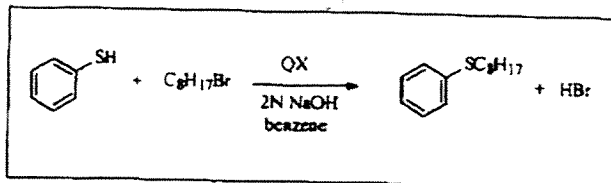
<sup>16</sup> McKillop, A.; Fiaud, J.; Hug, R.; Tetrahedron, 1974, 30, 1379

<sup>17</sup> Merz, A.; Angew. Chem. Int. Ed. Eng., 1973, 12, 846

<sup>18</sup> Wu, H.; Lai, J.; Ind. Eng. Chem. Res., 1995, 34, 1536

phosphonium salts and a crown ether which gave rate constants 20-30% higher.

Table 7: Effect of Catalyst on S-Alkylation



| catalyst                 | $k_{obs} \times 1000 \text{ l/Msec}$ |
|--------------------------|--------------------------------------|
| Bu <sub>4</sub> P Br     | 37                                   |
| Aliquat 336 <sup>®</sup> | 31                                   |
| TBAB                     | 5.2                                  |
| Pr <sub>4</sub> N Br     | 0.0056                               |
| TEBA Br                  | < 0.0016                             |

Reaction conditions: 2.0115g OctBr, 3.0171g PhSH, 1.0047g C<sub>14</sub>H<sub>28</sub>, 40 mL PhH, 0.00137 mol catalyst, 50mL 2N NaOH, 30°C

### Example Reactions - Oxidation

H<sub>2</sub>O<sub>2</sub> can be transferred into organic solvents by incorporation into the "hydration" shell of a quat-anion pair. The transfer of H<sub>2</sub>O<sub>2</sub> into CH<sub>2</sub>Cl<sub>2</sub> by quat salts is shown in Table 8.<sup>19</sup>

Table 8: Effect of Catalyst on H<sub>2</sub>O<sub>2</sub> Transfer

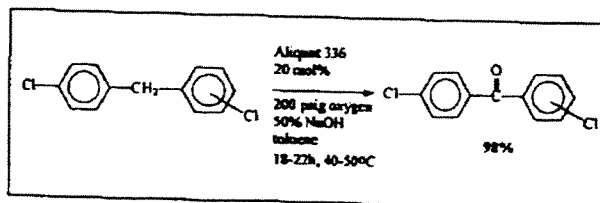
| quat salt                | $\frac{\text{equiv H}_2\text{O}_2 \text{ transferred}}{\text{equiv quat salt}}$ |
|--------------------------|---|
| Oct <sub>4</sub> N Br    | 1.00  |
| Aliquat 336 <sup>®</sup> | 0.88  |
| TBA Br                   | 0.68  |
| TBA Cl                   | 0.3   |
| TBAHSO <sub>4</sub>      | 0.1   |
| TEBA Cl                  | 0.013   |

Aliquat 336<sup>®</sup> appears to be the best commercially available quat for hydrogen peroxide transfer. In fact, hydrogen peroxide epoxidations are performed using Aliquat 336<sup>®</sup>.<sup>20,21</sup> They usually require the addition of tungstate/phosphate to stabilize the peroxide.

The first hypochlorite oxidations were reported using TBAHSO<sub>4</sub> as the catalyst.<sup>8</sup>

Activated hydrocarbons can be oxidized by deprotonation with concentrated NaOH and reaction with oxygen.<sup>22</sup> Aliquat 336<sup>®</sup> and TBAHSO<sub>4</sub> again were the best commercially available catalysts (see Table 9). The maximum conversion resulted from a combination of organophilicity, counteranion and stability factors.

Table 9: Effect of Catalyst on Base-Promoted Oxidation



| quat salt                | maximum conversion |
|--------------------------|--------------------|
| Aliquat 336 <sup>®</sup> | 98%                |
| Oct <sub>4</sub> N Br    | 93%                |
| TBA HSO <sub>4</sub>     | 90%                |
| TBA Br                   | 67%                |
| TEBA Cl                  | 44%                |

### Example Reactions - Hydrolysis

The saponification of diethyl adipate showed great sensitivity to both counteranion and quat structure (see Table 10).<sup>23</sup> The effect of counteranion in this case is the greatest since hydroxide transfer is difficult (affecting [QOH]<sub>org</sub>) though not rate determining. Catalyst decomposition would not be a significant factor in this reaction which was performed at room temperature. These results cause one to wonder how effective would be Aliquat 336<sup>®</sup> if it had an HSO<sub>4</sub> counteranion.

Table 10: Effect of Catalyst on Hydrolysis

| catalyst                 | yield |
|--------------------------|-------|
| TBAHSO <sub>4</sub>      | 93%   |
| Aliquat 336 <sup>®</sup> | 50%   |
| TBA Cl                   | 32%   |
| TBA Br                   | 18%   |
| TEBA Cl                  | 18%   |

Reaction conditions: 10 mmol diethyl adipate, 50 mmol 50% NaOH, 5mL pet ether, 0.2mol% catalyst, 1h, r.t.

<sup>19</sup> ref 5, p. 522 and reference cited therein

<sup>20</sup> Au, A.; (Dow Chemical) 1991 US Patent 5,036,154

<sup>21</sup> Venturello, C.; Alneri, E.; Lana, G.; 1981 Ger. Offen. 3,027,349

<sup>22</sup> Halpern, M.; Lysenko, Z.; J. Org. Chem., 1989, 54, 1201

<sup>23</sup> Dehmlow, E.; Barahona-Naranjo, S.; J. Chem. Res. (S), 1979, 238

### Example Reactions - Dehydrohalogenation

The mechanism of PTC dehydrohalogenations has been the subject of debate and firm conclusions have not been widely accepted. Therefore, it is difficult to predict the effect of catalyst. Empirically, several interesting observations have been made regarding the effect of catalyst. Early dehydrobrominations were performed with TBAHSO<sub>4</sub>. The use of TBAHSO<sub>4</sub> in dehydrobrominations sometimes requires the use of stoichiometric amounts of quat.<sup>24</sup> Dehydrobromination of 2-phenethylbromide proceeded well catalytically with Oct<sub>4</sub>N Br and slowly with TEBA Br.<sup>25</sup> Didehydrobromination to obtain alkynes could be performed catalytically only with highly organophilic quats such as Aliquat 336<sup>®</sup> and tetraoctylammonium bromide.<sup>26</sup> TBAHSO<sub>4</sub> and TEBAC did not didehydrobrominate under catalytic conditions. Dehydrochlorinations proceed well with TBAHSO<sub>4</sub>.<sup>27</sup> A patent reported the dehydrochlorination of an adduct of dichlorosuccinate.<sup>28</sup> This dehydrochlorination has a strong driving force to conjugate two carbonyl groups. Under comparative conditions, Aliquat 336<sup>®</sup> gave 78% yield, MeNBu<sub>3</sub> Cl gave 56% yield and TEBAC gave 8% yield. TBA Cl was screened in the early stages of the project but was not evaluated under the final set of comparative conditions.

The largest volume dehydrochlorinations are performed using  $\beta$ -hydroxyalkyl quats.<sup>29</sup> Such quats should be screened based on the optimization literature published.<sup>30</sup> However, these are highly specialized quats and may not be appropriate for determining if your candidate dehydrohalogenation will work during the first experiment. In other work, highly reactive dehydrobromination was observed when a "third phase" could be formed using TBAB.<sup>31</sup> Careful adjustment of temperature and concentration needed to be manipulated to obtain the third phase. The search for a third phase during an optimization stage is a very useful practice because it can lead to great improvements in process profitability, however, it should not be the target of a first experiment. Again, for

screening experiments, we want to choose a phase-transfer catalyst which is likely to work catalytically for the widest variety of dehydrohalogenations. The only catalyst which qualifies is Aliquat 336<sup>®</sup>.

### Example Reactions - Transition Metal Co-Catalysis

There is little in the literature to suggest which catalyst should be chosen for transition metal co-catalyzed PTC ("PTC/TM") reactions. All three classic quats (Aliquat 336<sup>®</sup>, TBA, TEBA) appear in the PTC/TM literature. Starks used tridecyl methyl ammonium chloride (Aliquat 336<sup>®</sup> is a 2:1 mixture of (C<sub>13</sub>:C<sub>10</sub>)<sub>2</sub>NMe Cl) in most of the PTC/TM oxidations reported in the classic PTC patent.<sup>11</sup> Alper's group performed many PTC/TM reactions,<sup>32</sup> including carbonylations using hydroxide. In the early years, they used primarily TEBAC<sup>33</sup> and more recently they use other catalysts (e.g., Hex<sub>4</sub>NHSO<sub>4</sub><sup>34</sup>). Carbonylations have also been performed using Aliquat 336<sup>®</sup>.<sup>35,36</sup> Sasson's and Blum's groups have coordinated RhCl<sub>3</sub> and PtCl<sub>4</sub> with Aliquat 336<sup>®</sup> to make Q<sup>+</sup>RhCl<sub>4</sub><sup>-</sup> and Q<sup>+</sup>PtCl<sub>6</sub><sup>-</sup> which are totally soluble in organic solvents and performed subsequent catalytic reactions.<sup>37,38</sup> Recent work on the Heck reaction used TBAHSO<sub>4</sub>/Br with excellent results.<sup>39</sup> Other work with palladium also used TBA salts.<sup>40,41,42</sup> Three publications actually screened a number of phase-transfer catalysts used with palladium. PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/formate was used in hydrodebromination and showed catalyst effectiveness as follows: Hex<sub>4</sub>NHSO<sub>4</sub> > Aliquat 336<sup>®</sup> > TBAHSO<sub>4</sub>.<sup>43</sup> In another hydrodebromination, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/benzyl alcohol was used and Aliquat 336<sup>®</sup> gave approximately double the maximum rate of reaction relative to TEBAC. TEBAC was slightly faster than Hex<sub>4</sub>NBr.<sup>44</sup> Hydrodechlorination with Pd/C and hydrogen showed

<sup>32</sup> Alper, H.; *Adv. Organomet. Chem.*, 1981, 183

<sup>33</sup> for example, Alper, H.; des Abbayes, H.; *J. Organomet. Chem.*, 1977, 134, C11

<sup>34</sup> Amaratunga, S.; Alper, H.; *J. Organomet. Chem.*, 1995, 488, 25

<sup>35</sup> Younis, K.; Amer, I.; *Organometallics*, 1994, 13, 3120

<sup>36</sup> Badrieh, Y.; Blum, J.; Schumann, H.; *J. Mol. Catal.*, 1994, 90, 231

<sup>37</sup> Sasson, Y.; Zoran, A.; Blum, J.; *J. Mol. Catal.*, 1981, 11, 293

<sup>38</sup> Baidossi, W.; Schumann, H.; Blum, J.; *Tetrahedron*, 1996, 52, 8349

<sup>39</sup> Jeffery, T.; Galland, J.; *Tetrahedron Lett.*, 1994, 4103

<sup>40</sup> Vlassa, M.; Ciocan-Tarta, I.; Margiucanu, F.; Oprcan, I.; *Tetrahedron*, 1996, 52, 1337

<sup>41</sup> Wang, J.; Hu, Y.; Cui, W.; *Synth. Commun.*, 1994, 24, 3261

<sup>42</sup> Choudary, B.; Reddy, N.; Ashok, B.; *Applied Catal.*, 1987, 32, 357

<sup>43</sup> Bar, R.; Sasson, Y.; Blum, J.; *J. Mol. Catal.*, 1982, 16, 175

<sup>44</sup> Hallgren, J.; Lucas, G.; *J. Organomet. Chem.*, 1981, 212, 135

<sup>24</sup> Gorgues, A.; Le Coq, A.; *Tetrahedron Lett.*, 1976 4723

<sup>25</sup> Halpern, M.; Ph.D. Thesis, 1983, Hebrew Univ of Jerusalem

<sup>26</sup> Dehmlow, E.; Lissel, M.; *Tetrahedron*, 1981, 1653

<sup>27</sup> Halpern, M.; Zahalka, H.; Sasson, Y.; Rabinovitz, M.; *J. Org. Chem.*, 1985, 50, 5088

<sup>28</sup> Maulding, D.; (American Cyanamid) 1989, US Patent 4,847,405

<sup>29</sup> Maurin, L.; (DuPont) 1983, US Patent 4,418,232

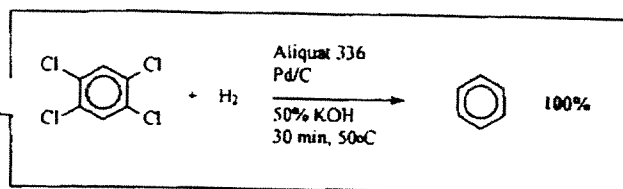
<sup>30</sup> Kurginyan, K.; *Mendeleev Chem. J. Eng. (Allerton)*, 1986, 31, 74

<sup>31</sup> Mason, D.; Magdassi, S.; Sasson, Y.; *J. Org. Chem.*, 1991, 56, 7229

highest reactivity with Aliquat 336<sup>45</sup>. A large phosphonium salt gave high conversion, but too large of an ammonium salt (60 carbons) decreased activity (see Table 11). TBAHSO<sub>4</sub> and TEBA Br were not effective.

Again, since clear guidelines are not available for choosing a catalyst for all PTC/TM reactions, the first experiment of a new PTC/TM screening program should probably be run with Aliquat 336<sup>46</sup> or possibly Hex<sub>4</sub>NHSO<sub>4</sub>.

Table 11 : Effect of Catalyst on Hydrodechlorination



| catalyst  | time (h) | % conversion |
|---|----------|--------------|
| Aliquat 336 <sup>46</sup>   | 0.5      | 100%         |
| C <sub>16</sub> H <sub>33</sub> PBu <sub>3</sub> Br                                 | 1.5      | 100%         |
| C <sub>16</sub> H <sub>33</sub> N(C <sub>18</sub> H <sub>37</sub> ) <sub>3</sub> Br | 1.5      | 63%          |
| TEBA Br   | 1.5      | no reaction  |
| TBAHSO <sub>4</sub>   | 2.0      | no reaction  |
| PEG-2000  | 1.5      | no reaction  |

### Reactions in Which TEBAC Excels

The discussion and data presented above relate to I-reactions and are not encouraging for TEBAC fans. With so much discouraging TEBAC data (reactivity and stability), how could this catalyst become so popular? The answer is because TEBAC truly is an outstanding catalyst for a great many PTC applications. Since Makosza first published the C-alkylation of phenylacetonitrile in 1965<sup>46</sup> using TEBAC, hundreds of PTC/OH applications have been published, patented and commercialized. Makosza himself used TEBAC in scores of synthetic publications<sup>47</sup> for C-alkylations, N-alkylations, carbene reactions and nucleophilic aromatic substitutions, even before Starks coined the term "phase-transfer catalysis." Some attribute the widespread use of TEBAC as a "shelf catalyst" for

screening new PTC applications, to Makosza's prolific publication of TEBAC.<sup>48</sup>

Instead of just using TEBAC to screen PTC/OH reactions, it would be desirable to be able to predict the effect of quat structure on PTC reactions which do not abide by the standard I-reaction criteria. Unfortunately, not enough is understood about non-I-reaction PTC systems to fully characterize them and predict optimal conditions with certainty. The mechanism(s) of PTC/OH reactions have always been the subject of great debate. It is thought that some combination of interfacial and extractive processes govern the course of PTC/OH reactions.<sup>1,49</sup> Conclusive evidence has been provided to show that interfacial tension is an important factor in at least one PTC/OH alkylation.<sup>50</sup> If a PTC reaction were transfer rate limited ("T-Reaction") then reduction of interfacial tension would enhance the reaction rate, regardless if the mechanism were interfacial or extractive. In contrast, since the rate determining step of an I-reaction is in the organic phase, the rate at which the anion crosses the phase boundary would be irrelevant history in determining the overall reactivity of the reaction. Interfacial tension is just one example of an effect of quat structure which would manifest itself quite differently for I-reactions vs T-reactions. It would not be surprising, therefore, to observe radically different reactivity behaviors of PTC systems based on quat structure.

We can use these observations to examine these anomalous PTC/OH systems<sup>51</sup> on an empirical basis. Other than "knowing" that TEBAC seems to work well for certain types of PTC/OH reactions, only a few studies were reported which compare a variety of catalysts. Two of these studies suggest empirical guidelines for THIS<sup>51</sup> category of PTC/OH reactions (the concepts of interfacial tension<sup>50</sup> and accessibility<sup>52</sup> to be discussed below).

<sup>48</sup> I must admit that I used TEBAC exclusively, following historical precedent, when I performed my first undergraduate PTC research in the 1970's. I was lucky that I did not choose to perform I-reactions in that early work or I may have been discouraged by the use of TEBAC and moved into some other field of chemistry for my career.

<sup>49</sup> Makosza, M., "Phase-Transfer Catalysis: Mechanism and Syntheses, ACS Symposium Series 659," Halpern, M. ed., American Chemical Society, Washington DC, 1997, Chapter 4

<sup>50</sup> Mason, D.; Magdassi, S.; Sasson, Y.; *J. Org. Chem.*, 1990, 55, 2714

<sup>51</sup> please note that not all PTC/OH reactions are anomalous; some PTC/OH systems are clearly I-reactions such as the isomerization of allylbenzene (ref 3)

<sup>52</sup> Halpern, M.; Sasson, Y.; Rabinovitz, M.; *Tetrahedron*, 1983, 38, 3183 and ref 25

<sup>45</sup> Marques, C.; Selva, M.; Tundo, P. *Gazz. Chim. Ital.*, 1996, 126, 317

<sup>46</sup> Makosza, M.; Serafinowa, B.; *Rocz. Chem.*, 1965, 39, 1223

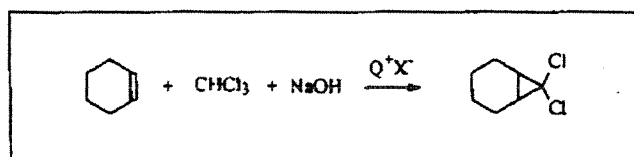
<sup>47</sup> Makosza, M.; *Pure Appl. Chem.*, 1975, 43, 439

### Example Reactions - Carbene Addition

The most comprehensive screening of catalysts for a PTC/OH reaction was reported by Dehmloew and Lissel.<sup>53</sup> The reaction studied was the reaction of cyclohexene with dichlorocarbene and dibromocarbene generated from chloroform and bromoform. They reported the results for 28 ammonium quats and 19 other phase-transfer catalysts. Data are presented for selected quats in Table 12.

TEBAC does seem to perform better than the other chlorides. Polarizable anions seem to reduce the reactivity. The homologous quat bromide series is difficult to interpret. Taking the broader perspective, it is clear that TEBAC is a good catalyst, as opposed to the I-reaction systems discussed earlier. It is interesting to note that the same study which was performed for the addition of dibromocarbene to cyclohexene showed smaller differences in reactivity between catalysts.

Table 12: Effect of Catalyst on Carbene Addition



| catalyst                           | yield | catalyst              | yield |
|------------------------------------|-------|-----------------------|-------|
| TEBA Cl                            | 51%   | Et <sub>4</sub> N Br  | 44%   |
| Aliquat 336®                       | 42%   | Pr <sub>4</sub> N Br  | 26%   |
| Bu <sub>4</sub> N Cl               | 39%   | Bu <sub>4</sub> N Br  | 29%   |
| Pr <sub>4</sub> N Cl               | 34%   | Pnt <sub>4</sub> N Br | 32%   |
|                                    |       | Hex <sub>4</sub> N Br | 35%   |
| Bu <sub>4</sub> N HSO <sub>4</sub> | 46%   | Hep <sub>4</sub> N Br | 28%   |
| Bu <sub>4</sub> N Cl               | 39%   | Oct <sub>4</sub> N Br | 23%   |
| Bu <sub>4</sub> N Br               | 29%   |                       |       |
| Bu <sub>4</sub> N I                | 23%   |                       |       |

Reaction conditions: 0.1 mol cyclohexene, 0.4 mol CHCl<sub>3</sub>, 0.2 mol 50% NaOH, 0.001 mol catalyst, 4h, 23°C

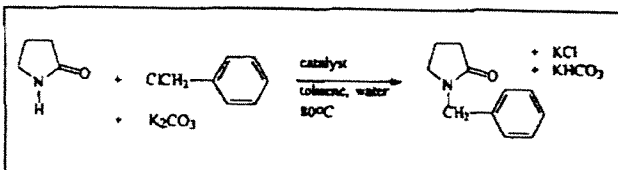
### Example Reactions - Alkylation

Alkylation reactions usually show clearer trends. The N-benylation of pyrrolidinone showed that TEBAC outperformed the larger catalysts (Table 13).<sup>54</sup>

In order to truly evaluate the effect of quat structure on a given reaction, it is important to systematically

change the structure of the catalyst, including non-symmetrical catalysts. Unfortunately, only one such study was reported (many studies report one homologous series or only symmetrical quats) and that was for the methylation of deoxybenzoin<sup>52</sup> (Table 14).

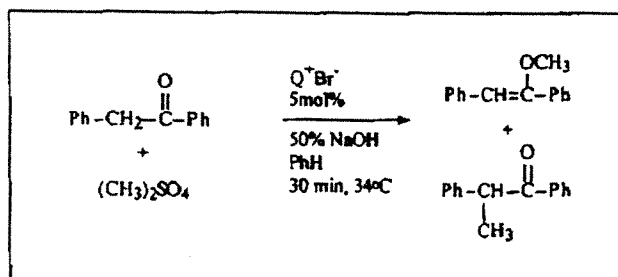
Table 13: Effect of Catalyst on N-Alkylation



| catalyst              | initial rate (mmol/dm <sup>3</sup> min) |
|-----------------------|---|
| TEBAC                 | 5.00                                    |
| TBAB                  | 2.49                                    |
| Hex <sub>4</sub> N Cl | 1.45                                    |

Reaction conditions: 25 mmol 2-pyrrolidinone, 25 mmol benzyl chloride, 50 mmol K<sub>2</sub>CO<sub>3</sub>, 2.5 mmol QX, 25 mL toluene, 80°C

Table 14: Effect of Catalyst on Alkylation



| quat salt              | conversion at 30 min              | q value |
|------------------------|-----------------------------------|---------|
| BuNEt <sub>3</sub> Br  | 100%                              | 1.8     |
| TEBA Br                | not measured (expected placement) |         |
| OctNEt <sub>3</sub> Br | 98%                               | 1.6     |
| MeNBu <sub>3</sub> Br  | 95%                               | 1.8     |
| Et <sub>4</sub> N Br   | 85%                               | 2.0     |
| EtNBu <sub>3</sub> Br  | 79%                               | 1.3     |
| MeNOct <sub>3</sub> Br | 67%                               | 1.4     |
| Bu <sub>4</sub> N Br   | 54%                               | 1.0     |
| EtNOct <sub>3</sub> Br | 47%                               | 0.9     |
| Pnt <sub>4</sub> N Br  | 45%                               | 0.8     |
| Hex <sub>4</sub> N Br  | 40%                               | 0.7     |
| BuNOct <sub>3</sub> Br | 36%                               | 0.6     |
| Oct <sub>4</sub> N Br  | 29%                               | 0.5     |
| Me <sub>4</sub> N Br   | 21%                               | 4.0     |

<sup>53</sup> Dehmloew, E.; Lissel, M.; Tetrahedron Lett., 1976, 1783

<sup>54</sup> Sasson, Y.; Bilman N.; J. Chem. Soc. Perkin Trans II, 1989, 2029



The qualitative concept of accessibility was proposed based on the observation of these data which show that the presence of even one methyl group or several ethyl groups resulted in higher reactivity (too much accessibility of the positive charge of  $\text{Me}_4\text{N}$  leads to so much hydrophilicity that the catalyst's function degrades significantly). Several years later a simple calculation was proposed to attempt to characterize accessibility: "q" = sum of the reciprocals of the number of carbons of each linear chain of the quat. Before the q value was suggested, it was obvious that alkyltriethyl ammonium quats were somehow structurally fit to catalyze this type of PTC/OH reaction well. The q value provided a means to compare non-symmetrical quats. For example, the q value of  $\text{MeNBu}_3$  was similar to that of the  $\text{RNEt}_3$  and gave similar reactivity. The q values of homologous series of  $\text{RNBu}_3$  and  $\text{RNOct}_3$  correlated well with the reactivities of these quats. The q value was suggested only as an empirical parameter. Reactivity of certain types of PTC/OH reactions seem to increase as the q value increased up to about 1.5-2 then decrease. **The commercially available quat which has the most carbons (good for I-reactions) and also has the closest q value to 1.5-2.0 (good for this category of PTC/OH reactions) is  $\text{MeNOct}_3$  (q = 1.4, C# = 25; similar to Aliquat 336®).** The quat with the next highest q value (below 1.5) and the most number of carbons is  $\text{Bu}_4\text{N}$  (q = 1.0, C# = 16).

#### Back to the Central Question... Which Catalyst Should I Try First?

The central question which the current article addresses is how to maximize the chances of making the first PTC experiment work. Therefore, it would be desirable to choose a catalyst which induces the highest reactivity possible in *both* categories of I-reaction and T-reaction. This is because *we cannot predict with certainty* if a reaction will be intrinsic reaction rate limited or transfer limited before we run the first experiment. Empirical examination of the PTC systems shown above for both I-reactions as well as T-reactions indicates that Aliquat 336® and TBA HSO<sub>4</sub> induce relatively high reactivity in both categories. In some cases, they may not induce as much reactivity as TEBAC, but they can certainly be chosen to **span the I-reaction and T-reaction categories.**

Despite the sensibility of the approach to focus on reactivity in the first experiment, the temptation still exists to find the "magic bullet" on the first experiment. Some chemists may prefer to screen Aliquat 336® first because it is much less expensive, more readily

available and more thermally stable than TBAHSO<sub>4</sub>. Aliquat 336® also will not be likely to contaminate aqueous waste streams because it is so organic soluble. Some chemists will compromise the reactivity of TBAHSO<sub>4</sub> and use TBAB instead, which is more competitive in price with Aliquat 336®. TBAB can often be separated from the product by water washing (which may or may not be desirable). Aliquat 336® is particularly suitable for commercial use when the product is distillable or recrystallizable. However, these considerations are beyond the scope of the discussion to determine which catalyst to use for the first experiment. Let's face it, you do have to choose a catalyst for the *first* experiment. So you might as well make an informed decision. It is recommended that you try either Aliquat 336® or TBAHSO<sub>4</sub>. Either of these two catalysts will give you the best shot at obtaining some product in the first experiment.

If *neither* Aliquat 336® nor TBAHSO<sub>4</sub> show promising results, then there is a decision tree to further evaluate the feasibility of the PTC process. If *either* Aliquat 336® or TBAHSO<sub>4</sub> show promising results, then there is a whole other decision tree to further evaluate the feasibility and optimize the PTC process. These decision trees start with the first experiment and are the keys to effective (high process performance) and efficient (short development time) PTC process research.

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#### About the Author - Dr. Marc E. Halpern

Dr. Marc E. Halpern is a leading authority on increasing profit for client companies using phase-transfer catalysis (PTC) technology. Dr. Halpern provides consulting and training which focus on all practical, theoretical and organizational aspects to identify opportunities, develop and implement PTC technology in commercial industrial processes. Dr. Halpern helped companies save > \$16 million/yr in process improvements. In 1995/6, Dr. Halpern provided consulting and training at > 50 industrial sites in the US, Europe, the Middle East and Asia.

Dr. Halpern authored/co-authored the classic books and training programs "Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives" (Chapman & Hall, 1994) "Enhancing Process Profitability Using Phase-Transfer Catalysis" (PTC Communications, Inc. 1995), "Practical Phase-Transfer Catalysis" (PTC Communications, Inc. 1996). Dr. Halpern composed the guidelines for evaluating and optimizing new PTC applications and invented the accessibility parameter for characterizing the effect of phase-transfer catalyst structure on reactivity and selectivity. Dr. Halpern has an impressive track record from Organic Process Chemist to Director, Research and Development over a 12 year period in the chemical industry.

**Exhibit D**

EASY AND EFFICIENT ANION ALKYLATIONS IN SOLID-LIQUID PTC CONDITIONS

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Abstract : Alkylation of anionic nucleophiles such as potassium acetate or potassium indole can be achieved in good yields without solvent either in the presence of  $\text{NBu}_4\text{Br}$  and small amounts of  $\text{TiO}_2$  or in the presence of Aliquat 336 ( $\text{Oct}_3\text{MeN}^+\text{Cl}^-$ ).

We describe here a new method for alkylating organic anions, which requires neither solvent nor solid support, and works in very mild conditions and with a very easy work-up. Two examples are selected which concern anions which either are stable (e.g.  $\text{CH}_3\text{COO}^-$ ) or must be obtained from their conjugated acid (e.g. the anion from indole).

ALKYLATIONS OF THE ACETATE ANION

The synthesis of esters by alkylation of carboxylate anions is usually performed using the silver or mercuric salt in a protic or ether solvent or, more recently, the sodium or potassium salt in dipolar aprotic solvents (1). Carboxylate alkylations can also be carried out using phase transfer catalysis (PTC) (2); however, formation of n-octyl acetate from  $\text{CH}_3\text{COO}^-$  and n-OctX requires temperatures higher than 80°C.

Very recently, alternative methods have been proposed :

- i) use of reagents impregnated on mineral solid supports (3),
- ii) gas-liquid PTC, at a temperature ca 150°C and under reduced pressure (20 Torr) (4),
- iii) use of polyethyleneglycols immobilized on  $\text{Al}_2\text{O}_3$  or  $\text{SiO}_2$  as PTC catalyst (5).

Our new methods are simpler :

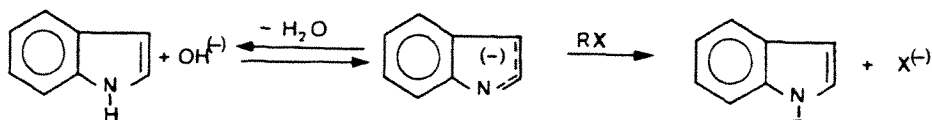
Method I : The reaction was carried out by simply mixing finely ground  $\text{CH}_3\text{COOK}$  with pure n-octyl bromide in the presence of 1 %  $\text{NBu}_4\text{Br}$  and small amounts of  $\text{TiO}_2$  ( $\text{TiO}_2$  : acetate = 0.2 w/w) (6). After stirring for 5 minutes, the mixture was heated at 60°C for 2 hours to afford n-octyl acetate in 93 % yield. This easy alkylation must certainly imply both an anionic activation of  $\text{CH}_3\text{COO}^-$  by  $\text{NBu}_4\text{Br}$  and an activation of n-OctBr by electrophilic assistance by  $\text{TiO}_2$ , resulting in a weakening of the C-Br bond.

Method II : By using Aliquat 336 (essentially  $\text{Oct}_3\text{MeN}^+\text{Cl}^-$ ) as the PTC catalyst, n-octyl acetate was obtained in 98 % yield (20 h - room temperature) even in the absence of  $\text{TiO}_2$ . Very good yields (> 93 %) in benzyl, allyl, n-butyl and cetyl acetates were observed in similar conditions.

The reaction products were easily recovered by simple filtration after addition of

ether. They were qualitatively and quantitatively analyzed by VPC (internal standard) and characterized by IR and NMR.

#### ALKYLATION OF POTASSIUM INDOLE



The N-alkylation of potassium indole is usually achieved using a dipolar aprotic solvent (DMSO, HMPA) (7) or PTC conditions (8).

To potassium indole prepared by stirring indole with 2.5 mole.eq of ground KOH for 5 minutes in the presence of 1 %  $\text{NBu}_4\text{Br}$ , was then added the pure alkylating agent (e.g.  $\text{EtI}$  or  $\text{Et}_2\text{SO}_4$ ) and the mixture was stirred for 10 minutes at room temperature. After addition of ether and filtration, N-ethyl indole was isolated in 98 % yield. The less reactive n-octyl bromide also reacted smoothly (2 h -  $50^\circ\text{C}$ ) to give N-octyl indole (yield : 98 %).

Addition of an organic solvent or mineral solid supports did not improve the yield and even proved, in some cases, to be prejudicial to the reaction (9) : for example excess  $\text{TiO}_2$  ( $\text{TiO}_2$  : acetate = 4),  $\text{Al}_2\text{O}_3$  or  $\text{SiO}_2$  inhibit the alkylation of  $\text{CH}_3\text{COOK}$  by n-OctBr ;  $\text{Al}_2\text{O}_3$  prevents N-alkylation of potassium indole by Et-I.

The procedures described here, in particular the one using Aliquat 336, are more efficient, less expensive and milder than those published previously, which require more lengthy procedures (3), higher temperatures (3-5) or low pressure conditions (4). We sincerely thank Dr J. SEYDEN-PENNE for very fruitful discussions.

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(Received in France 23 September 1982)

**Exhibit E**

# Anionic Activation by Solid-Liquid Phase Transfer Catalysis Without Solvent: An Improvement in Organic Synthesis

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(Received 26 February 1984)

Nowadays, and more than ever, organic synthesis involves economical (cost of materials, solvents and energy) and environmental (toxicity, pollution) problems. Therefore, performing organic reactions without solvent, efficiently and economically, is of interest.

The aims of this article are:

(a) to emphasize the possibility of performing many organic reactions, dealing with anionic activation, *in the absence of organic solvent*;

(b) to advocate solid-liquid phase transfer catalysis (PTC) without solvent;

(c) to indicate that many reactions can be carried out without solvents under very mild conditions and with an easy work-up, giving high yields at comparatively low temperatures (very often at room temperature); in some cases in competitive reactions, performed under these conditions, selectivity is observed.

In this paper, we shall compare our results with those obtained using other methods for anionic activation. It is known that an efficient anionic activation is obtained when the nucleophilic anion  $N^-$  is not solvated, and when the ion pair  $NM^+$  is effectively dissociated. This is achieved by the use of homogeneous reactions in polar aprotic solvents (expensive, often toxic and difficult to remove); by classical PTC methods [1-4], i.e., generally in the presence of organic solvents such as benzene, toluene, methylene chloride, chloroform, etc.; anionic activation reactions can also be conducted with supported reagents on mineral solids (alumina, silica clays, etc.).

We became interested in mineral support utilization for anionic activation through the work of E. Keinan and Y. Mazur [5] (1977), which deals with the oxidation of a nitro group into carbonyl (Nef reaction) on "basic" silica gel. This work showed that nitro compound adsorbed on the solid support, in the absence of organic solvent ("dry media"), generates a nitronate anion which leads to a carbonyl group. Mazur and co-workers extended this methodology to other types of reactions performed on silica, including oxidation with oxygen atoms [6a], ozone [6b], or  $FeCl_3$  [6c].

Since 1979, we have undertaken a systematic study of anionic activation reactions on solid inorganic supports (carboxylates, cyanide, fluoride, etc.). Alkaline salts of stable anions are directly impregnated on the support

(alumina being the more effective), while salts of non-stable anions are generated in situ on support by reacting a base with the conjugated acid of the anion (malonate, acetoacetate, phenoxides, etc.). The alkylations of these supported anionic species are very efficient and involve milder reaction conditions, simpler work-up and higher selectivity than when run in organic solvents. We have also reported [8] the reduction of carbonyl and  $\alpha,\beta$ -unsaturated carbonyl compounds by  $M^+BH_4^-$  ( $M^+ = Li^+, Na^+, K^+, NBu_4^+$ ) on solid inorganic supports in "dry media" conditions; we observed that the reaction rate decreases when a solvent (diethyl ether) was added, without any change in the selectivity (1-2 versus 1-4 reduction for  $\alpha,\beta$ -unsaturated ketones). The selectivity is different from that observed in an ethereal solution, and this fact is indicative that reaction occurs on the support, even when a solvent is present.

As already pointed out, alumina was the most effective support for alkylation, but the yield of the alkylation of  $CH_3CO_2K^+$  by  $nC_8H_{17}Br$  on silica gel could be significantly improved by adding small amounts of a quaternary ammonium salt ( $NBu_4HSO_4$ , or, much better,  $C_{16}H_{33}N(CH_3)_3Br$ ) to the support. When a quaternary ammonium grafted silica (Spherosil QMA, Rhone-Poulenc) is used as the support, a dramatic increase of the reaction rate is observed. We proposed an interpretation based on the nature of the superficial charge of the solid, however, cation exchange may also be considered.

We then undertook a systematic study of the nature and of the amount of the mineral support. It appears that solid  $CH_3CO_2K^+$ , finely ground, reacts with an equimolecular quantity of alkylating agent in the presence of a catalytic amount of tetrakyl ammonium salt. *Neither solvent nor support are necessary for the reaction.* Yields thus obtained compared favourably with those derived from the use of alumina as support or with those obtained by other methods recently described. The reaction conditions are very mild (often room temperature) and the work-up is simple: after vigorous stirring for 10 min with a mechanical stirrer, the mixtures are left aside at the appropriate temperature. After reaction completion, organic products are eluted by simple filtration on Florisil (on which ammonium salts remain adsorbed) with diethyl ether or dichloromethane. Proof

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| Method   | Ester |                 | AcOCH <sub>2</sub> -CH=CH <sub>2</sub> | AcO <sub>n</sub> C <sub>n</sub> H <sub>n</sub> |            | AcO <sub>n</sub> C <sub>n</sub> H <sub>11</sub> |             | AcOCH <sub>2</sub> Ph   |       | AcO <sub>n</sub> C <sub>n</sub> H <sub>13</sub> |           |            |            |
|--|-------|-----------------|--|--|------------|---|-------------|-------------------------|-------|---|-----------|------------|------------|
| Our results [10]                                       | 2h    | RT <sup>a</sup> | 98%                                    | 10h<br>2h                                      | RT<br>60°C | 93%<br>98%                                      | 20h<br>2h   | RT <sup>†</sup><br>60°C | 2h    | RT  | 30h<br>3h | RT<br>75°C | 92%<br>98% |
| Reactions on alumina without solvent ("dry media")     |       |                 |  | 20h  | 85°C       | 50% [7b]  | 5h          | 85°C                    |       |   | 20h       | 85°C       | 88%        |
| Reactions on alumina in presence of toluene or benzene |       |                 |  |  |            |   | 91h<br>100h | 90°C<br>90°C            |       |   |           |            |            |
| Solid-liquid CTP                                       |       |                 |  |  |            |   | 3h          | 83°C                    | 2h    | 25°C  |           |            |            |
| Liquid-liquid CTP                                      | 46h   | 25°C            | 90%                                    |  |            |   |             |                         | 0.25h | 25°C  |           |            |            |
| Gas-liquid CTP   |       |                 |  |  |            |   |             |                         |       | 150°C<br>(20 mm Hg)                             |           |            |            |
| PEG 400 grafted silica + toluene                       |       |                 |  | 3h   | 110°C      | 56% [25]  |             |                         |       |   |           |            |            |

a. RT = room temperature.

We will now describe some results obtained by extending this approach to anionic reactions, mainly alkylations.

$$\underset{\text{solid}}{\text{CH}_3\text{CO}_2\text{M}^+} + \underset{\text{liquid}}{\text{R}'\text{X}} \xrightarrow{\text{NR}_4^+\text{X}^-} \underset{\text{liquid}}{\text{RCO}_2\text{R}'} + \underset{\text{solid}}{\text{M}^+\text{X}^-}$$

Alkyl acetates are obtained in very good yields. Two quaternary ammonium salts were examined as catalysts,  $\text{NBu}_4\text{Br}$  and Aliquat 336; the latter compound, which consists essentially of  $(\text{C}_8\text{H}_{17})_3\text{NCH}_2\text{Cl}$  [11], is known as one of the most efficient PTC catalysts in liquid-liquid [12] and in solid-solid [13] conditions.

Aliquat 336 is far superior to  $\text{NBu}_4\text{Br}$  for acetate alkylation performed with  $\text{nC}_4\text{H}_9\text{Br}$ ,  $\text{nC}_8\text{H}_{17}\text{Br}$  and  $\text{nC}_{16}\text{H}_{33}\text{Br}$ : *alkyl acetates are thus obtained with yields >92% at room temperature*. For the reactions involving  $\text{PhCH}_2\text{Br}$  and  $\text{Br}(\text{CH}_2)_3\text{Cl}$ , or  $\text{CH}_2=\text{CH}-\text{CH}_2-\text{Br}$ , the relative efficiency of  $\text{NBu}_4\text{Br}$  and aliquat is the same ( $\text{NBu}_4\text{Br}$  being slightly superior to aliquat). In both cases, a quasiquantitative yield is obtained at room temperature. Using  $\text{Br}(\text{CH}_2)_3\text{Cl}$  as a reagent, Br is specifically displaced by the acetate anion. In alkylations with n-octyl halides, leaving group sequence  $\text{Br} > \text{Cl} > \text{I}$  was observed, similar to that of some PTC reactions, and different from that previously observed in homogeneous reactions [11,14].

Two explanations can be proposed for this effect:

- (i) A lower solubility of  $\text{CH}_3\text{CO}_2\text{NR}_4^+$  in alkyl iodides
- (ii) A solubility of the ammonium iodide which is formed in the reaction, and thus an inhibition of the PTC process, as previously proposed [14,15].

Only a few examples of solid-liquid PTC without added solvent [16-19] can be found in the literature. In 1967, H.E. Hennis described the synthesis [16] of some alkyl carboxylates, the catalysts being tertiary amines or quaternary ammonium salts. However, higher temperatures were needed with Hennis's method than with ours to obtain good yields. For example, to reach 98% of benzyl acetate, 2h at 125°C was required with Hennis' method, and only 2h at room temperature with ours to obtain 99% of this product.

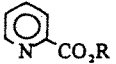
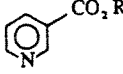

Table 1 shows the best results obtained by us, compared with those obtained by utilization of other recent methods of anionic activation leading to alkylacetate synthesis. Formate anion alkylation, leading to alkyl formates, are under current investigation by Y. Sasson and H.A. Zahalka [26].

Alkyl esters can also be prepared from aromatic carboxylates, and good yields are obtained under very mild conditions, which compare favourably with those used in other methods (Table 2).

Table 2. Synthesis of Alkyl Benzoates by Alkylation of Benzoates Anions: Comparison of Recent Methods

| Ester   | $C_6H_5CO_2iPr$ |      |     | $pNO_2-C_6H-CO_2Et$ |      |     | $C_6H_5-CO_2(CH_2)_4O_2C-C_6H_5$ |       |     |
|---|-----------------|------|-----|---------------------|------|-----|----------------------------------|-------|-----|
| Method  |                 |      |     |                     |      |     |                                  |       |     |
| Our results   | 24h             | 60°C | 92% | 6h                  | RT   | 95% | 12h                              | 40°C  | 86% |
| $C_6H_5CO_2H + Resin \dot{N}(CH_3)_3OH$<br>+ $iPrBr$ in hexane [28] | 13h             | 50°C | 60% |                     |      |     |                                  |       |     |
| $pNO_2-C_6H_4CO_2H + EtOH$<br>+ $(CH_3)_3SiCl$ in THF [29]          |                 |      |     | 48h                 | 78°C | 81% |                                  |       |     |
| $C_6H_5CO_2H/KF + Br(CH_2)_4Br$<br>in DMF [30]                      |                 |      |     |                     |      |     | 0.5h                             | 130°C | 85% |
| $C_6H_5CO_2K + Br(CH_2)_4Br$ in DMF [30]                            |                 |      |     |                     |      |     | 1h                               | 140°C | 80% |

Table 3. Synthesis of Pyridine Carboxylic Esters by Alkylation of Carboxylates Anions [31]

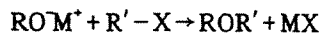
| Ester                           |  |      |      |  |      |     |  |      |     |
|---------------------------------|---|------|------|---|------|-----|---|------|-----|
| Alkylating agent (catalyst 10%) |   |      |      |   |      |     |   |      |     |
| $Et_2SO_4 (NBu_4Br)$            | 24h   | RT   | 51%  | 24h   | RT   | 24% | 24h   | RT   | 29% |
| $EtBr (NBu_4Br)$                | 48  | RT   | 32%  | 43h   | RT   | 81% | 43  | RT   | 93% |
| $PhCH_2Cl (NBu_4Br)$            | 20h   | RT   | 68%  | 24h   | RT   | 81% | 24h   | RT   | 74% |
| $nC_8H_{17}Br (Aliquat)$        | 24h   | 85°C | 100% | 48h   | 60°C | 93% | 24h   | 60°C | 93% |
| $nC_{16}H_{33}Br (Aliquat)$     | 72h   | 60°C | 90%  | 72h   | 60°C | 90% | 72h   | 60°C | 96% |

A problem of selectivity arises with alkylation of pyridine-carboxylates owing to the competitive quaternization of the pyridine ring. Nevertheless, good yields of esters were obtained when a suitable leaving group was selected for the alkylating electrophile (Table 3). As previously observed, Aliquat 336 is the best catalyst for  $nC_8H_{17}Br$  and  $nC_{16}H_{33}Br$ , while  $nBu_4Br$  is more efficient for  $Et_2SO_4$ ,  $EtBr$  and  $PhCH_2Br$ .

## II. ETHER SYNTHESIS

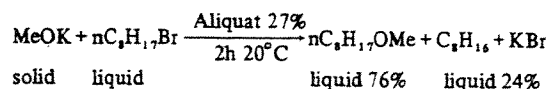
### (a) Aliphatic Ethers [32]

The best general method for ether synthesis is still the alkoxides alkylation (Williamson reaction) [33].

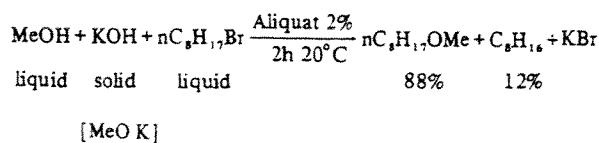


Three possibilities of an access of disymmetric ROR' ethers were investigated, and are described below.

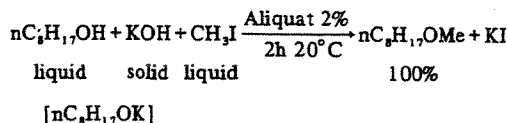
**Method A.** Alkylation by  $nC_8H_{17}Br$  performed with alkoxides, technical or prepared in aqueous or methanolic solution ( $MeONa$ ,  $MeOK$ ,  $EtONa$ ,  $tBuOK$ ):



**Method B.** Alkylation of *in situ* generated alkoxides performed with  $nC_8H_{17}Br$ :



**Method C.** Alkylation of *in situ* generated  $nOctOK^+$  performed with  $MeI$ .



Evidently, the last method is the best one, as no competitive elimination (octene formation) takes place with  $MeI$  as alkylating agent.

Results obtained for  $nC_8H_{17}OMe$  synthesis by means of other recently described methods are also indicated in Table 4.

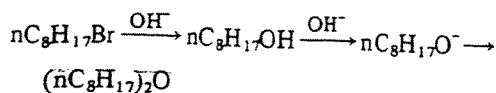
It is apparent that the use of  $KOH/Aliquat$  without solvent is the best method; not only is it very easy to perform and inexpensive, but the yield is quantitative within 2 h at room temperature. It also avoids the use of heavy cations such as  $Hg$  or  $Tl$  (highly toxic), or expensive aprotic solvents, and takes place under very mild and efficient conditions.

Table 4. Recent Methods for Synthesis of  $nC_8H_{17}OCH_3$  ( $nC_8H_{17}OH + base + ICH_3$ )

| Base                                    | Solvent    | Time (h) | Temp. | Yield |
|---|------------|----------|-------|-------|
| $KOH/Aliquat 2\%$ [32]<br>(our results) | no solvent | 24       | RT    | 100%  |
| $KF/Alumina$ [34]                       | $CH_3CN$   | 40       | RT    | 90%   |
| $NaOH/nBu_4I 2\%$ [35]                  | $C_6H_6$   | 4        | 45°C  | 90%   |
| $TIOEt$ [36]                            | $C_6H_6$   | 14       | RT    | 26%   |
| $KOH$ [37]                              | DMSO       | 0.5      | RT    | 83%   |



It is possible to prepare aliphatic disymmetric ethers without solvent, by reaction of generated alkoxides ( $\text{ROH} + \text{KOH}$ ) *in situ*, in the presence of a PTC catalyst. Thus, the reaction of  $n\text{C}_8\text{H}_{17}\text{Br}$  with an excess of  $\text{KOH}$  under this condition at  $100^\circ\text{C}$  for 7 h, leads to 57% yield of dioctyl ether.



This result is comparable to the classical liquid-liquid PTC reaction using aqueous  $\text{NaOH}$  and benzene at  $80^\circ\text{C}$  for 4 h, resulting in 75% yield. We performed the reaction  $n\text{C}_8\text{H}_{17}\text{OH} + \text{KOH} + n\text{OctBr}$  in the presence of 2% Aliquat 336 for 2 h at room temperature, obtaining 98% of the isolated ether  $(\text{nC}_8\text{H}_{17})_2\text{O}$ . These conditions are milder and more efficient than those described in the classical PTC reaction which utilizes aqueous  $\text{NaOH}$  and benzene, and results in 75% yield after 8 h at  $70^\circ\text{C}$ .

#### A Peculiar Case: *t*-BuOK

*t*-BuOK, a strong base, generally leads to large amounts of elimination products. However, in the reaction to *t*-BuOK with  $n\text{C}_8\text{H}_{17}\text{Br}$ , using different PTC catalysts and Aliquat 336, no elimination occurred. The last compound was shown to be the most effective.

As in  $\text{E}_2$  and  $\text{SN}_2$  type reactions, the effect of temperature and catalyst on the elimination is limited. On the other hand, the effect of the leaving group is considerable, as observed in homogenous reactions. Thus,  $\beta$ -elimination is favoured when iodide is a leaving group whereas  $\text{SN}_2$  type reaction is favoured when tosylate is a leaving group.

#### (b) Aromatic Ethers [31, 70]

Aryl ethers are also obtained in high yields (Table 5) without solvent under solid-liquid PTC conditions. In this reaction, phenoxide anions are formed *in situ* with solid  $\text{KOH}$ , and then alkylated with alkyl halides in "one pot" reaction.

In this case, the yields and the reaction conditions compare favourably with previously described methods (Table 6).

It is significant that long chain halides can also be used with very good results.

### III. SYNTHESIS OF ALKYL CYANIDES

Cyanide alkylation is presently under investigation. From preliminary results, it appears that alkyl cyanides can be very easily prepared under mild conditions, *but only in the presence of 1 eq. of water*. Thus  $\text{KCN}$  reacts (8 h,  $20^\circ\text{C}$ ) with 1 eq.  $\text{Br}(\text{CH}_2)_5\text{Br}$  in presence of 2% Ali-

Table 5. Synthesis of Aromatic Esters [32]








| $\text{ArOH} + \text{KOH} + \text{RX} \xrightarrow{2\% \text{ Aliquat}} \text{ArOR}$                         |  |          |                    |       |
|--|--|----------|--------------------|-------|
| ArOH   | RX                                     | Time (h) | Temp.              | Yield |
|                           | $\text{CH}_3\text{I}$                  | 5        | RT                 | 99%   |
|                           | $n\text{C}_8\text{H}_{17}\text{Br}$    | 2        | $85^\circ\text{C}$ | 98%   |
|                           | $n\text{C}_{16}\text{H}_{33}\text{Br}$ | 6        | $85^\circ\text{C}$ | 92%   |
|                           | $n\text{C}_4\text{H}_9\text{Br}$       | 2        | $60^\circ\text{C}$ | 100%  |
| $\text{CH}_3\text{-CO-}$  | $n\text{C}_8\text{H}_{17}\text{Br}$    | 2        | $85^\circ\text{C}$ | 97%   |
| $\text{O}_2\text{N-}$     | $\text{CH}_3\text{I}$                  | 2        | $85^\circ\text{C}$ | 97%   |
|                           | $n\text{C}_8\text{H}_{17}\text{Br}$    | 2        | $85^\circ\text{C}$ | 97%   |

Table 6. Synthesis of Phenylbutyl Ether: Comparison of Recent Methods ( $\text{PhO}^- + n\text{C}_4\text{H}_9\text{Br}$ )

| Method                              | Solvent                  | Time (h) | Temp.                               | Yield |
|-------------------------------------|--------------------------|----------|-------------------------------------|-------|
| Our results [31]                    | no solvent               | 2        | $60^\circ\text{C}$                  | 100%  |
| Liquid-liquid CTP [40]              | $\text{CH}_2\text{Cl}_2$ | 12       | RT                                  | 85%   |
| Gas-liquid CTP [41]                 | no solvent               |          | $170^\circ\text{C}$<br>(p: 10 Torr) | 68%   |
| Triphase catalysis [42]             | toluene                  | 2        | $110^\circ\text{C}$                 | 99%   |
| Triphase catalysis [43]             | toluene                  | 72       | $100^\circ\text{C}$                 | 71%   |
| Triphase catalysis [44]             | toluene                  | 12       | $110^\circ\text{C}$                 | 60%   |
| $\text{PhO}^-$ exchanged resin [45] |                          | 6        | $50^\circ\text{C}$                  | 100%  |

quat and 1 eq.  $\text{H}_2\text{O}$  to give quantitatively the dinitrile. No reaction takes place in the absence of water. This preparation of  $\text{NC}(\text{CH}_2)_3\text{CN}$  is obviously more efficient than those previously described, for instance, classical solid-liquid PTC (3 h, toluene reflux, 70%) [46], or KCN impregnated on alumina reaction (48 h,  $85^\circ\text{C}$ , 71% [7b]). Similarly, the reaction of KCN with  $\text{PhCH}_2\text{Br}$  gives, in the presence of 1 eq.  $\text{H}_2\text{O}$  and 2% Aliquat, 99% yield of  $\text{PhCH}_2\text{CN}$  (2 h,  $20^\circ\text{C}$ ) [71].

#### IV. SYNTHESIS OF ALKYL FLUORIDES AND RELATED COMPOUNDS

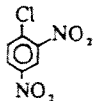
Classical PTC methods lead to an increase in the anionic reactivity of fluoride. However, the "activated" fluoride anion behaves both as a nucleophile and a base, resulting in a competition between substitution, elimination and hydrolysis. These methods necessitate severe experimental conditions [1-4].

M. Tordeux and C. Wakselman very recently described [47] the preparation of aryl fluorides and fluoroformates using solid-liquid PTC conditions without solvent, and with  $(\text{C}_2\text{H}_5)_3\text{NCH}_2\text{PhBr}^-$  as a catalyst. Under these conditions calcinated KF reacts very poorly with cyclochlorides or chromoformates. However, the efficiency of the reaction is considerably increased when KF absorbs  $\text{H}_2\text{O}$  in ~1% of its weight. The effect of a small amount of water on reactivity of fluoride was also observed by S. Dermiek and Y. Sasson [48] who described fluoride anion alkylation in solid-liquid PTC without solvent. Under these conditions, KF in presence of catalytic amount of  $\text{NBu}_4\text{Br}$  and 0.5 eq.  $\text{H}_2\text{O}$  reacted ( $120^\circ\text{C}$ , 6h) with  $\text{nC}_8\text{H}_{17}\text{Cl}$  and gave 93% of  $\text{nC}_8\text{H}_{17}\text{F}$ . Their results also clearly demonstrate that the catalyst decomposition due to the basic reactivity of the fluoride anion intervenes in the direct fluorination.

We have also performed fluoride alkylation under related conditions [31]. KF appeared quite unreactive at the temperatures we used ( $T < 85^\circ\text{C}$ ). However, after addition of 1 eq. of water, the yield of alkyl fluoride increased. Although elimination reaction and the formation of ethers also occurred under these conditions, the latter were formed from fluoride mediated alkylation of the alcohol formed by hydrolysis of the halide.

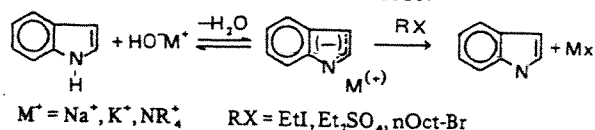
Nevertheless, we were able to obtain high yields of alkyl fluorides and related compounds when working under our usual conditions with CsF or  $\text{NBu}_4\text{F}$ ,  $3\text{H}_2\text{O}$  as the source of fluoride anion (Table 7). The reactions

Table 7. Reactions of Fluoride Anion

| $\text{FM}^+ + \text{RX} \xrightarrow{\text{Aliquat 10\%}} \text{R-F}$ |   |          |                    |       |
|--|---|----------|--------------------|-------|
| $\text{FM}^+$  | RX  | Time (h) | Temp.              | Yield |
| CsF  | $\text{PhCH}_2\text{Br}$  | 3        | $85^\circ\text{C}$ | 98%   |
| CsF  | $\text{nC}_8\text{H}_{17}\text{Br}$   | 40       | $85^\circ\text{C}$ | 77%   |
| CsF  | $\text{nC}_{16}\text{H}_{33}\text{Br}$  | 65       | $85^\circ\text{C}$ | 80%   |
| CsF  | $\text{BrCH}_2\text{CO}_2\text{Et}$   | 6        | $40^\circ\text{C}$ | 80%   |
| $\text{NBu}_4\text{F}$ , $3\text{H}_2\text{O}$                         |  | 2        | $20^\circ\text{C}$ | 45%   |

with ethyl bromoacetate and with 2,4-nitrochlorobenzene are noteworthy. The yields and the reaction conditions compare favourably with those described previously, but the use of CsF or  $\text{NBu}_4\text{F}$ ,  $3\text{H}_2\text{O}$  is certainly a limiting factor for this method.

#### V. INDOLE ALKYLATION



Indole alkylation requires the formation of the anion. This was easily done by mixing and stirring, for 5 min, indole with 2.5 eq. KOH (finely ground) and 1%  $\text{NBu}_4\text{Br}$ , and then adding 1.1 eq. of the alkylating electrophile (halide or sulfate). The effect of the quaternary ammonium salt is two-fold: (1) it induces the strong  $\text{NBu}_4\text{OH}$ , and thereby the anion; (2) it increases the nucleophilicity of the indole anion which is associated with the large  $\text{NBu}_4$  cation. Thus, with solid-liquid PTC, without solvent, N-alkylated indole derivatives are obtained quantitatively under very mild conditions. Better yields are obtained using KOH rather than NaOH as solid base (Table 8).

#### VI. ALKYLATION OF MALONATE ANION

In 1978, M. Makosza et al. described [49] an efficient alkylation of malonate and other anions using solid-liquid two-phase systems in the absence of solvent. They used anhydrous  $\text{K}_2\text{CO}_3$  or  $\text{Na}_2\text{CO}_3$  to deprotonate the conjugate acids of the nucleophilic anion crown ether, or  $\text{NBu}_4\text{Br}$  or  $\text{NEt}_4\text{Br}$  as catalyst. The reactions were performed at  $90-150^\circ\text{C}$  for 1-5 h.

Using  $\text{tBuOK}$  as the base and Aliquat or  $\text{NBu}_4\text{Br}$  (1-10%) as the catalyst, we prepared [31] (Table 9)

Table 8. N-alkylation of Indole

| $\text{Indole} + \text{KOH} + \text{RX} \xrightarrow{\text{NBu}_4\text{Br 1\%}} \text{N-alkylindole}$ |            |                    |       |
|---|------------|--------------------|-------|
| RX  | Time (min) | Temp.              | Yield |
| $(\text{C}_2\text{H}_5)_2\text{SO}_4$   | 10         | RT                 | 99%   |
| $\text{C}_2\text{H}_5\text{I}$  | 10         | RT                 | 95%   |
| $\text{nC}_8\text{H}_{17}\text{Br}$   | 120        | $50^\circ\text{C}$ | 98%   |

Table 9. Synthesis of Monoalkyl Malonates

| $\text{CH}_2(\text{CO}_2\text{Et})_2 + \text{tBuOK} + \text{RX} \xrightarrow{\text{NR}_4^+\text{X}^-} \text{R-CH}(\text{CO}_2\text{Et})_2$ |                             |          |       |       |  |
|--|-----------------------------|----------|-------|-------|--|
| RX   | $\text{NR}_4^+\text{X}^-$   | Time (h) | Temp. | Yield |  |
| $\text{C}_2\text{H}_5\text{Br}$  | $\text{NBu}_4\text{Br}$ 3%  | 24       | RT    | 96%   |  |
| $\text{CH}_3\text{CH-Br}$  | $\text{NBu}_4\text{Br}$ 3%  | 48       | RT    | 100%  |  |
| $\text{nC}_4\text{H}_9\text{Br}$   | $\text{NBu}_4\text{Br}$ 3%  | 24       | RT    | 87%   |  |
|  | Aliquat 3%                  | 24       | RT    | 85%   |  |
| $\text{nC}_8\text{H}_{17}\text{Br}$  | $\text{NBu}_4\text{Br}$ 3%  | 30       | RT    | 84%   |  |
|  | Aliquat 3%                  | 30       | RT    | 80%   |  |
| $\text{nC}_{16}\text{H}_{33}\text{Br}$   | Aliquat 10%                 | 30       | RT    | 98%   |  |
|  | $\text{NBu}_4\text{Br}$ 10% | 30       | RT    | 80%   |  |

monoalkyl malonates (ethyl, isopropyl, n-butyl, benzyl, n-octyl and n-cetyl) by solid-liquid PTC without solvent. The reactions take place at room temperature and excellent yields are obtained after 1–30 h, depending on the halide. The selectivity is good and with a ratio monoalkylated products: dialkylated products >16, which compares favourably with results previously obtained. It is noteworthy that Aliquat is the most effective catalyst when long chain halide ( $C_{18}H_{33}Br$ ) was used.

#### VII. $\beta$ -ELIMINATIONS [72]

We have extended solid-liquid PTC without solvent to base-induced  $\beta$ -eliminations. Secondary halide dehydrogenations are well known in solution [50] or under classical PTC conditions. 2-Bromooctane was studied as a typical weak halide which may undergo either Saitzeff or Hofmann type elimination.

Aliquat appears to be the most efficient catalyst (quasiquantitative  $\beta$ -elimination is observed at room temperature) but the direction of elimination (1-octene/2-octenes) is only slightly affected by the nature of the ammonium salt. On the other hand, direction of elimination is strongly dependent on the nature of the base; the 1-octene/2-octenes ratios increases in the sequence  $tBuO^+ > OH^- > EtO^- > MeO^-$ .

We observed that *tBuOK* indicated eliminations are quantitative after 20 h at room temperature in the absence of any ammonium salt, but they can be catalyzed by 2% Aliquat (reaction completion within 2 h). With any other bases, no reaction takes place for 20 h at room temperature unless 2% Aliquat is added, resulting in yields >92%. Regioselectivity of elimination at room temperature under our conditions are very close to those obtained when the reactions are performed at reflux in alcoholic media. Our results, using *tBuOK*, are very similar to those obtained in the *tBuOH* solution [51a], but are very different to the results in DMSO [51b] or when classical PTC reactions were used [1–4].

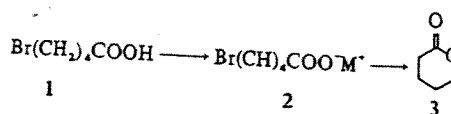
On Table 10 some of our results are indicated as well as those obtained from experiments performed in solvents under PTC and related conditions.

Table 10. Recent Methods for Dehydrohalogenation of 2-Bromooctane

| Basic reactants                                | Time (h)           | Temp. | Yield |
|--|--------------------|-------|-------|
| KF + phosphonium salts [52]                    | 76                 | 102°C | 64%   |
| KF + crown-ether ( $C_6H_6$ ) [53]             | ( $t_{1/2}$ =240h) | 90°C  | 68%   |
| polymer supported $F^-$ [54]                   | 30                 | 36°C  | 73%   |
| <i>tBuOK</i> + crown ether [55]                | 3                  | 60°C  | 76%   |
| (petroleum ether)                              |                    |       |       |
| NaOH + $NBu_4Br$ ( $H_2O-C_6H_6$ ) [56]        | 48                 | 80°C  | 86%   |
| KOH/crown-ether ( $C_6H_6$ ) [57a]             | 18                 | 80°C  | 80%   |
| KOH + PEG 600 ( $C_6H_6$ ) [57a,b]             | 2                  | 80°C  | 82%   |
| KOH + PEG 600 + crown-ether ( $C_6H_6$ ) [56b] | 2                  | 80°C  | 100%  |
| KOH + Aliquat 2% [50]                          | 20                 | RT    | 93%   |
| <i>tBuOK</i> without catalyst [50]             | 20                 | RT    | 94%   |
| <i>tBuOK</i> + Aliquat 2% [50]                 | 2                  | RT    | 92%   |
| MeOK + Aliquat 2% [50]                         | 20                 | RT    | 95%   |
| EtONa + Aliquat 2% [50]                        | 20                 | RT    | 92%   |

#### VIII. EXAMPLES OF ALKYLATIONS

##### (a) Intramolecular Alkylation: Synthesis of $\delta$ -Valerolactone [73]



5-Bromopentanoic acid is added to 1 eq. of finely ground base NaOMe, *tBuOK* or  $K_2CO_3$  in the presence of 2% Aliquat or in its absence. After 2 h at 40°C,  $\delta$ -valerolactone is isolated after addition of diethyl ether to the reaction mixture, and filtration on Florisil. Among the bases,  $K_2CO_3$  was found to be the best one; the stronger bases promoted ring opening of  $\delta$ -valerolactone. In the absence of Aliquat, 81% yield was obtained, but in its presence, the yield increased to 98%. Under these conditions, no intermolecular reactions were observed which could lead to polylactones.

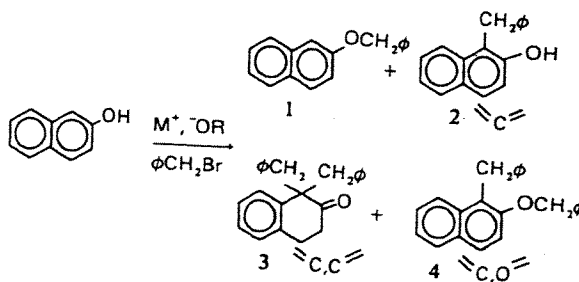
These yields are similar to those obtained by classical homogeneous cyclizations carried out under high dilution with cesium salt in DME [58] or with pyridine thiol ester in  $C_6H_6$  at reflux [59].

This method appears to be complementary to the one of Y. Kimura and S.L. Regen described very recently [60] and in which potassium salt of  $\omega$ -bromoacid is cyclized in toluene at 90°C in the presence of catalytic amounts of tetralkyl ammonium salts. In our hands, this procedure gave rise to only 27% of  $\delta$ -valerolactone. On the other hand, Kimura and Regen procedure is superior to ours for 7 member lactone (92% yield vs 30% under our experimental conditions).

Nevertheless, the possibility to mimic high dilution conditions by simple adsorption of a reagent on a reactive mineral support is noteworthy, and may have some theoretical and practical consequences.

##### (b) Alkylation of $\beta$ -Naphthoxide Anion [74]

$\beta$ -Naphthoxide anion is a typical phenolic ambident anion [61c]; its alkylation with  $PhCH_2Br$  may lead to four products:



It has been known since the pioneering experiments of N. Kornblum [61] that solvent is a very important factor for the orientation effect in this alkylation: O-alkylation is favoured in polar, aprotic solvents, while C-alkylation in protic solvents. Under liquid-liquid PTC conditions, some O-alkylation was observed [62] but alkylation on alumina in "dry media" [7b,c] led to significant C-alkylations. However, no efficient selective

Table 11: Alkylation of  $\beta$ -Naphthoxyde Anion

| a       | Base                  | Time (h) | Temp. | 1 "O"                             | 2 "C"                             | 3 "C,C"                           | 4 "C,O"                           |
|---------|-----------------------|----------|-------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| 1:1:1   | KOH-Aliquat (40%)     | 3        | 60°C  | 85 <sup>b</sup> (75) <sup>c</sup> |                                   |                                   |                                   |
| 1:2:2   | LiOH                  | 2        | 85°C  |                                   | 96 <sup>b</sup> (87) <sup>c</sup> |                                   | 7 <sup>b</sup>                    |
| 1:3:3   | LiOtBu                | 2        | 85°C  |                                   |                                   | 88 <sup>b</sup> (80) <sup>c</sup> | 10 <sup>b</sup>                   |
| 1:1:5:1 | 2 + KOH-Aliquat (40%) | 2        | 85°C  |                                   |                                   | 12 <sup>b</sup>                   | 85 <sup>b</sup> (74) <sup>c</sup> |

a. Ratio naphthol/base/PhCH<sub>2</sub>Br. b. Yield by VPC. c. Yield in isolated product.

method for formation at different alkylated products exists.

We were able to perform four very selective reactions, each leading almost exclusively to only one of the four possible alkylation products (Table 11). All reactions are performed without solvent; O-alkylation are Aliquat catalyzed solid-liquid PTC reactions, KOH being anion-generating base. C-alkylated products are prepared in the absence of ammonium salt, but with LiOH or tBuOLi as the base. When the latter base is used, di-C-alkylated  $\beta$ -naphthol is formed, whereas LiOH results in the mono-C-alkylated product. These results are important not only because of their excellent selectivity, but also because they are performed (1 h, at 85°C), without solvent and catalysis.

#### PTC Processes Conducted in the Absence of Organic Solvent

(a) *Liquid-Liquid PTC*. Many examples may be found in the literature [63,64] about liquid-liquid PTC reactions performed without the presence of solvent. Generally, the neat electrophile, sometimes present in excess, constitutes the organic phase [65]. It was observed that the presence of an organic solvent produced a considerable decrease in the reaction rate. Recently, Y. Sasson and H.A. Zahalka [66] have studied the catalyst poisoning effect in liquid-liquid PTC alkylation of aqueous HCO<sub>2</sub>Na by alkyl chlorides, and found that this poisoning effect is minimized when highly concentrated formate solutions are used. The presence of an aqueous phase appears to have no advantage with regard to solid-liquid PTC processes.

(b) *Gas-Liquid PTC*. Gas-liquid PTC reactions were recently described by P. Tundo et al. [24,67a]. These reactions are performed at high temperatures and pressures at which electrophile is in gaseous phase, and the catalyst in a liquid one. This new technique, which is performed under continuous flow conditions, could be of practical interest, for example, in the Wittig reaction.

#### The Role of Water

Several groups [47,68] have pointed out the importance of small amounts of water in solid-liquid PTC reactions. This effect of water is also important in solid-liquid PTC without solvent reactions, such as in fluoride and cyanide displacements. Water weakens the ionic interactions in the crystal, resulting in easier cation exchange with the catalyst and giving rise to nucleophilic anionic species associated with an ammonium cation. The lattice energies for CH<sub>3</sub>CO<sub>2</sub>K (686 kJ mol<sup>-1</sup>) and

CNK (669 kJ mol<sup>-1</sup>) [69] are similar, but the former reacts more efficiently, under our conditions, in the absence of water. It is possible that the formation of a local aqueous phase [68] saturated with the nucleophilic salt which is in equilibrium with the solid phase involved, in which case the reaction would take place in the liquid-liquid interface. However, this would not explain the specificity of KCN compared with CH<sub>3</sub>CO<sub>2</sub>K. On the other hand, the solubilities of the potassium salts in water and of the ammonium salts in the halides may play an important rôle.

In this account, we wanted to point out that solid-liquid PTC without solvent reactions have several important advantages over the reactions performed in the presence of solvents. They proceed efficiently under milder conditions, very often at room temperature; their work-up is simple and easy. In the case of competitive reactions, a selectivity is often observed.

*Acknowledgment.* The results we report here are part of a collaborative work. The valuable contributions of Dr. J. Barry, Dr. G. Decodts, Mr. A. Petit, Mr. P. Pigeon and Mr. F. Vaziri-Zand are acknowledged.

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